

PREVALENCE OF EXTRA INTESTINAL MANIFESTATIONS IN ULCERATIVE COLITIS

Original Research

Anam Tanveer^{1*}, Aisha Jamil¹, Someja Iqbal¹

¹Pakistan Emirates Military Hospital, Rawalpindi, Pakistan.

Corresponding Author: Anam Tanveer, Pakistan Emirates Military Hospital, Rawalpindi, Pakistan. anamtanveer.94@gmail.com

Acknowledgement: The authors sincerely appreciate the contributions of all study participants and the medical staff involved in data collection and patient care.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease primarily affecting the colon but frequently associated with extra-intestinal manifestations (EIMs), which can involve the musculoskeletal, ocular, dermatological, hepatobiliary, and renal systems. These manifestations significantly impact disease prognosis and patient quality of life. The prevalence and distribution of EIMs vary across populations, and their relationship with disease severity and duration remains a subject of ongoing investigation. Early identification and appropriate management of EIMs are crucial in optimizing patient outcomes.

Objective: To determine the prevalence of EIMs in UC patients and assess their association with disease severity, duration, and demographic factors.

Method: This cross-sectional study included 157 UC patients diagnosed based on clinical, endoscopic, histopathological, and radiological criteria. Demographic and clinical data, including disease duration and severity (assessed using the Mayo Score), were recorded. Patients were systematically evaluated for the presence of EIMs, categorized into musculoskeletal (arthritis, spondyloarthritis, osteopenia/osteoporosis), ocular (uveitis, episcleritis), dermatological (erythema nodosum, pyoderma gangrenosum), hepatobiliary (primary sclerosing cholangitis, non-alcoholic fatty liver disease), renal (nephrolithiasis), and other systemic manifestations (oral ulcers, thromboembolic events). Statistical analyses, including chi-square and t-tests, were performed to explore associations between EIMs and disease severity, duration, and gender distribution, with a p-value <0.05 considered statistically significant.

Results: EIMs were present in 42.7% (67/157) of patients. Musculoskeletal manifestations were the most prevalent (18.4%), with peripheral arthritis affecting 12.7% and spondyloarthritis 5.7%. Dermatological EIMs were observed in 12.8%, including erythema nodosum (8.3%) and pyoderma gangrenosum (4.5%). Ocular involvement was reported in 10.2%, with uveitis in 6.4% and episcleritis in 3.8%. Hepatobiliary manifestations affected 14.1%, with primary sclerosing cholangitis in 4.5% and non-alcoholic fatty liver disease in 9.6%. Renal manifestations (nephrolithiasis) were present in 2.5%, while other systemic complications, including oral ulcers (5.1%) and thromboembolic events (3.8%), were also noted. EIMs were significantly associated with severe disease activity ($p < 0.05$) and longer disease duration, particularly in patients with UC for more than 10 years ($p = 0.01$). No significant gender differences were found in the overall prevalence of EIMs, though musculoskeletal EIMs were slightly more common in males and dermatological manifestations in females. Patients with EIMs reported significantly lower quality of life scores (60.3 ± 13.5 vs. 75.6 ± 10.2 , $p < 0.001$).

Conclusion: Extra-intestinal manifestations are prevalent in UC patients, with a strong correlation to disease severity and duration. These manifestations contribute to substantial morbidity and significantly impair quality of life. Early recognition and a multidisciplinary approach to managing EIMs are essential in improving patient outcomes.

Keywords: Arthritis, disease severity, extra-intestinal manifestations, inflammatory bowel disease, prevalence, quality of life, ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that primarily affects the colon and rectum. While it is predominantly characterized by gastrointestinal symptoms, a significant proportion of patients develop extra-intestinal manifestations (EIMs) that impact various organ systems, including the musculoskeletal, ocular, dermatological, and hepatobiliary systems. These manifestations can emerge before, during, or after the diagnosis of UC, often complicating disease management and affecting the overall prognosis (1). Despite advancements in understanding UC, the prevalence, underlying mechanisms, and clinical implications of EIMs remain subjects of ongoing research. Estimates suggest that approximately 25% of UC patients experience at least one EIM, highlighting the need for heightened awareness and comprehensive care strategies (2). Joint involvement, particularly peripheral arthritis and spondyloarthritis, is among the most frequently reported EIMs, with an estimated prevalence of 10-20%. These conditions often correlate with disease activity, causing significant morbidity and impacting quality of life (3). Similarly, ocular manifestations, such as uveitis and episcleritis, occur in approximately 5-10% of patients and may lead to serious complications if left untreated (4). Dermatological conditions, including erythema nodosum and pyoderma gangrenosum, frequently signal increased disease severity, reinforcing their role as important clinical indicators (5). Involvement of the hepatobiliary system, particularly primary sclerosing cholangitis (PSC), represents a severe EIM associated with an increased risk of colorectal cancer and liver cirrhosis, affecting approximately 2-7% of UC patients (6). The pathophysiology underlying these manifestations is complex and multifactorial, involving genetic predisposition, immune dysregulation, and environmental triggers that contribute to systemic inflammation (7).

Given the broad spectrum of EIMs and their impact on disease course, a multidisciplinary approach to UC management is essential. The presence of these manifestations necessitates vigilant screening, early diagnosis, and tailored interventions to prevent long-term complications and improve patient outcomes. Addressing both intestinal and extra-intestinal symptoms in an integrated manner remains a crucial aspect of UC care. However, gaps persist in understanding the precise mechanisms driving these associations, necessitating further research to refine therapeutic strategies and optimize disease management (8). This study aims to provide a comprehensive overview of the prevalence and clinical significance of EIMs in UC, emphasizing the necessity for proactive screening, early intervention, and personalized treatment approaches. By advancing knowledge in this area, the research seeks to contribute to improved patient care and long-term disease management strategies (9).

METHODS

This cross-sectional, observational study was conducted at PEMH Rawalpindi from June 2024 to November 2024. All patients diagnosed with ulcerative colitis (UC) who attended the outpatient and inpatient departments during this period were included, and data was collected prospectively. Ethical approval was obtained from the Institutional Review Board (IRB) of CMH Rawalpindi, and informed consent was secured from all participants prior to data collection. The sample size was determined using the WHO sample size calculator, with a 95% confidence interval, a 5% margin of error, and a reported UC prevalence of 11.55% in Pakistan, resulting in a final sample of 157 patients (11). Patients aged 18 years and older with a confirmed diagnosis of UC based on clinical, endoscopic, histopathological, and radiological findings were eligible for inclusion. Those with a history of other inflammatory bowel diseases, such as Crohn's disease, or incomplete medical records were excluded to ensure diagnostic specificity. Demographic and clinical data, including age, sex, disease duration, and comorbidities, were recorded systematically. Disease activity was assessed using a validated scoring system, such as the Mayo Score, and severity was categorized as mild, moderate, or severe based on standard clinical criteria.

The primary objective was to determine the prevalence and spectrum of extra-intestinal manifestations (EIMs) in UC patients. EIMs were classified into musculoskeletal (peripheral arthritis, spondyloarthritis, osteopenia/osteoporosis), ocular (uveitis, episcleritis, conjunctivitis), dermatological (erythema nodosum, pyoderma gangrenosum, other skin disorders), hepatobiliary (primary sclerosing cholangitis, fatty liver disease, cirrhosis), renal (nephrolithiasis, other renal disorders), and other systemic manifestations, including thromboembolic events and oral ulcers. Patients were systematically evaluated for these manifestations through clinical examination, laboratory investigations, and imaging studies. Ocular and dermatological conditions were confirmed through referrals to ophthalmology and dermatology specialists. Hepatobiliary involvement was assessed using liver function tests, ultrasonography, and, where necessary,

liver biopsy or cholangiography for primary sclerosing cholangitis confirmation. Musculoskeletal manifestations were diagnosed based on clinical findings supported by radiological imaging, including X-rays, MRI, or ultrasound, as indicated. Data analysis was performed using descriptive and inferential statistical methods. Continuous variables were summarized as means with standard deviations (SD), while categorical variables were presented as frequencies and percentages. Associations between EIMs and demographic or clinical variables such as age, sex, and disease severity were analyzed using chi-square tests for categorical variables and independent t-tests for continuous variables. A p-value of <0.05 was considered statistically significant. This study adhered to ethical guidelines outlined in the Declaration of Helsinki. Patient confidentiality was maintained by anonymizing all collected data. Informed consent was obtained from all participants, ensuring their voluntary participation and right to withdraw at any stage without consequences for their medical care. Ethical clearance details, including IRB reference number, were documented as per institutional regulations.

RESULTS

A total of 157 patients diagnosed with ulcerative colitis (UC) were included in the study, with a mean age of 38.5 years (SD = 12.4). The cohort comprised 86 males (54.8%) and 71 females (45.2%). The mean disease duration was 8.3 years (SD = 4.2), with disease activity classified as mild in 68 patients (43.3%), moderate in 55 patients (35.0%), and severe in 34 patients (21.7%) based on the Mayo Score.

Table: Demographic Characteristics of UC Patients

| Characteristic | Value |
|------------------|-----------------------|
| Total Patients | 157 |
| Mean Age (years) | 38.5 $\hat{\pm}$ 12.4 |
| Male | 86 (54.8%) |
| Female | 71 (45.2%) |

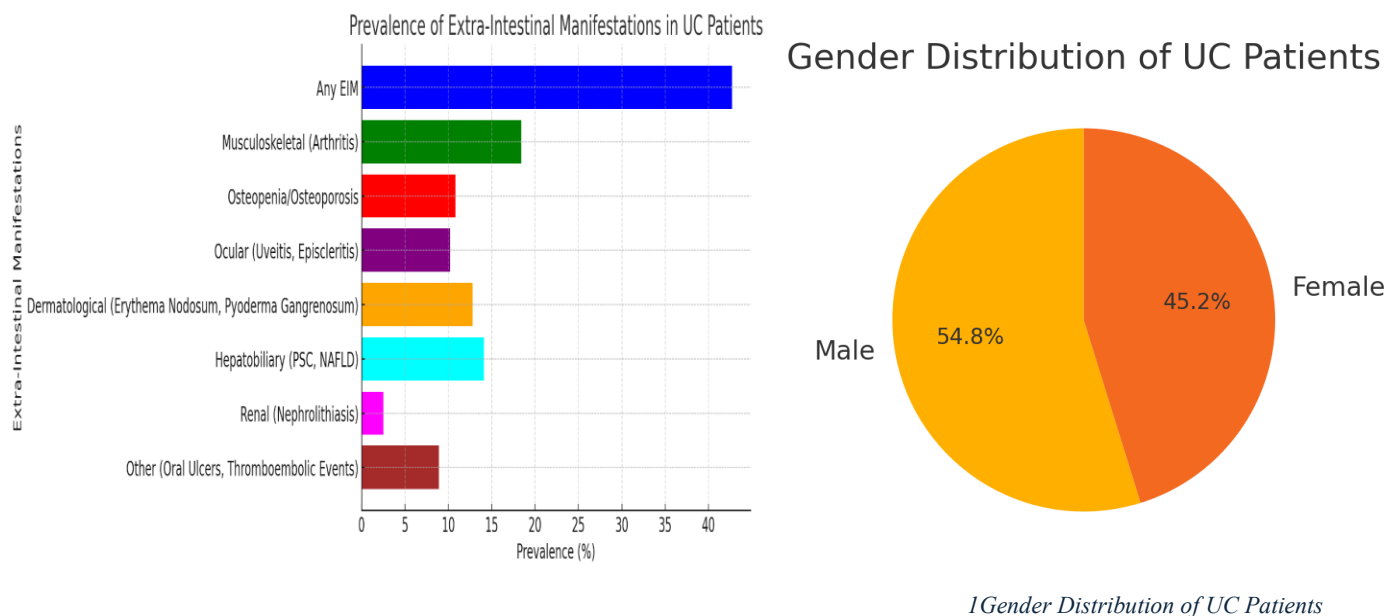
Extra-intestinal manifestations (EIMs) were present in 42.7% (67/157) of patients, with musculoskeletal manifestations being the most prevalent. Arthritis was observed in 18.4% (29/157) of patients, of whom 12.7% (20/157) had peripheral arthritis and 5.7% (9/157) had spondyloarthropathy. Osteopenia or osteoporosis was detected in 10.8% (17/157) of patients, particularly among those with prolonged disease duration and higher disease activity. Ocular manifestations were reported in 10.2% of patients, with uveitis diagnosed in 6.4% (10/157) and episcleritis in 3.8% (6/157). Dermatological manifestations were noted in 12.8% of patients, including erythema nodosum in 8.3% (13/157) and pyoderma gangrenosum in 4.5% (7/157). Other dermatological conditions, such as psoriasis and dermatitis, were present in 3.2% (5/157).

Table: Prevalence of Extra-Intestinal Manifestations

| Manifestation | Prevalence (%) |
|---|----------------|
| Any EIM | 42.7 |
| Musculoskeletal (Arthritis) | 18.4 |
| Osteopenia/Osteoporosis | 10.8 |
| Ocular (Uveitis, Episcleritis) | 10.2 |
| Dermatological (Erythema Nodosum, Pyoderma Gangrenosum) | 12.8 |
| Hepatobiliary (PSC, NAFLD) | 14.1 |
| Renal (Nephrolithiasis) | 2.5 |
| Other (Oral Ulcers, Thromboembolic Events) | 8.9 |

Hepatobiliary involvement was identified in 14.1% of patients, with primary sclerosing cholangitis (PSC) diagnosed in 4.5% (7/157), all of whom had moderate to severe UC. Non-alcoholic fatty liver disease (NAFLD) was observed in 9.6% (15/157), confirmed by abnormal liver enzyme levels. Renal manifestations were less frequent, with nephrolithiasis reported in 2.5% (4/157). Other systemic manifestations included oral ulcers in 5.1% (8/157) and thromboembolic events, such as deep vein thrombosis and pulmonary embolism, in 3.8% (6/157). A significant association was observed between disease severity and the presence of EIMs. Patients with severe disease had a higher prevalence of musculoskeletal ($p = 0.03$), dermatological ($p = 0.04$), and ocular manifestations ($p = 0.02$). The frequency of EIMs was also significantly higher among patients with UC duration exceeding 10 years ($p = 0.01$). Among those with severe UC, arthritis was the most frequently observed EIM (30.3%), followed by uveitis (12.1%). In contrast, patients with mild UC exhibited a lower overall prevalence of EIMs (30.9%), with erythema nodosum (6.3%) and peripheral arthritis (7.4%) being the most common manifestations.

No statistically significant differences were found in the overall prevalence of EIMs between male and female patients. However, musculoskeletal involvement, particularly peripheral arthritis, was slightly more frequent in males, whereas dermatological manifestations, including erythema nodosum, were more common in females. Patients with EIMs reported a significantly lower quality of life compared to those without, as measured by the EQ-5D score (mean score 60.3 ± 13.5 vs. 75.6 ± 10.2 , $p < 0.001$). The most frequently reported symptoms affecting quality of life included joint pain, vision impairment, and dermatological lesions, which contributed to considerable physical and psychological distress.



DISCUSSION

The findings of this study demonstrated that extra-intestinal manifestations (EIMs) are prevalent in ulcerative colitis (UC) patients, affecting 42.7% of the cohort. This prevalence is consistent with prior studies that have reported similar rates of EIMs in UC populations, reinforcing the systemic nature of the disease and its impact beyond the gastrointestinal tract (12). Musculoskeletal manifestations were the most commonly observed EIMs, followed by dermatological, ocular, and hepatobiliary involvement. The significant association between EIMs and disease severity, as well as disease duration, highlights the importance of early recognition and comprehensive management strategies to improve patient outcomes. Musculoskeletal involvement, particularly arthritis, was the most frequently reported EIM, affecting 18.4% of UC patients. This prevalence aligns with existing literature, which suggests that arthritis occurs in approximately 10–30% of UC cases (13). Peripheral arthritis was more common than spondyloarthritis, a pattern that has been consistently observed in previous studies (14). The strong association between arthritis and UC severity, with a significantly higher prevalence among patients with severe disease ($p = 0.03$), further supports the notion that systemic inflammation in UC may contribute to joint pathology (15). Given the impact of arthritis on mobility and daily functioning, these findings emphasize the need for multidisciplinary care involving rheumatologists to optimize patient management.

Ocular manifestations, including uveitis and episcleritis, were reported in 6.4% and 3.8% of patients, respectively. These findings are in accordance with previous research indicating that ocular complications occur in 2–12% of UC patients (16). The higher prevalence of uveitis in moderate to severe disease is consistent with existing evidence, which suggests that increased systemic inflammation may contribute to the development of ocular involvement (17). Uveitis, in particular, poses a risk for significant visual impairment and requires early detection and intervention to prevent complications (18). The results further reinforce the need for routine ophthalmologic evaluation in UC patients, particularly those with more aggressive disease. Dermatological manifestations were identified in 12.8% of patients, with erythema nodosum and pyoderma gangrenosum being the most commonly observed conditions. The reported prevalence aligns with previous studies that have documented similar rates of skin involvement in UC (19). Erythema nodosum, which was observed in 8.3% of patients, has been linked to disease activity and often serves as an indicator of disease exacerbation (20). Pyoderma gangrenosum, though less frequent (4.5%), is recognized as a more severe dermatological complication that can be refractory to treatment, particularly in patients with active disease (21). These findings underscore the need for dermatological assessment in UC patients presenting with cutaneous symptoms to facilitate prompt and targeted interventions.

Hepatobiliary involvement, particularly primary sclerosing cholangitis (PSC), was observed in 4.5% of patients, aligning with previous estimates of PSC prevalence in UC, which range from 2% to 7% (22). The presence of PSC in UC is of particular concern due to its established association with an increased risk of colorectal cancer and liver cirrhosis, necessitating regular liver function monitoring and surveillance (23). The results further highlight the importance of integrating hepatobiliary assessments into routine UC management, particularly for patients with prolonged disease duration or abnormal liver enzyme levels. Renal manifestations were relatively uncommon, with nephrolithiasis observed in 2.5% of patients. Although the prevalence of kidney stones in UC remains low, prior research has suggested that chronic inflammation, altered gut microbiota, and increased oxalate absorption contribute to an elevated risk of nephrolithiasis in patients with IBD (24). While renal involvement in UC is not as widely studied as other EIMs, these findings suggest the necessity of monitoring renal function in patients with long-standing disease.

The significant impact of EIMs on patient-reported quality of life highlights the broader implications of these manifestations beyond physical symptoms. Patients with EIMs reported significantly lower EQ-5D scores compared to those without, indicating greater impairment in mobility, pain levels, and overall well-being ($p < 0.001$). Similar findings have been reported in other studies, emphasizing that EIMs are a major contributor to the morbidity of UC (25). Joint pain, vision impairment, and skin lesions were the most frequently reported factors affecting daily functioning, underscoring the need for holistic disease management that extends beyond gastrointestinal symptom control. No significant gender differences were identified in the overall prevalence of EIMs, although male patients exhibited a slightly higher incidence of musculoskeletal involvement, while dermatological manifestations were more frequently observed in females. This minor variation is in agreement with previous research that has suggested subtle sex-based differences in the distribution of EIMs, though no substantial disparities in overall prevalence have been consistently documented (26).

The strong association between EIMs and disease duration further supports the hypothesis that chronic systemic inflammation plays a pivotal role in the pathogenesis of these complications. Patients with UC for more than 10 years exhibited a significantly higher prevalence of EIMs, a finding consistent with previous studies that have reported a cumulative increase in EIMs with prolonged disease duration (27). The precise mechanisms underlying this association remain poorly understood, but immune dysregulation, genetic susceptibility, and persistent inflammatory pathways are believed to contribute to the development of extra-intestinal involvement (28). While this study provides valuable insights into the prevalence and clinical characteristics of EIMs in UC, certain limitations must be acknowledged. The study was conducted at a single center, which may limit the generalizability of findings to broader UC populations. Additionally, the reliance on clinical and radiological assessments for EIM diagnosis may introduce variability in detection rates, particularly for conditions with subtle or intermittent presentations. Future studies should consider multicenter designs with larger sample sizes and standardized diagnostic criteria to enhance the reliability and applicability of findings. Furthermore, longitudinal studies assessing the progression of EIMs over time and their response to specific therapeutic interventions would provide deeper insights into the optimal management strategies for affected patients. These findings underscore the necessity for comprehensive and multidisciplinary care in UC, integrating gastroenterology, rheumatology, dermatology, ophthalmology, and hepatology expertise to address the full spectrum of disease complications. Early detection and targeted management of EIMs can significantly improve patient outcomes and quality of life, highlighting the importance of vigilant monitoring in clinical practice.

CONCLUSION

This study underscores the substantial burden of extra-intestinal manifestations in patients with ulcerative colitis, emphasizing their strong association with disease severity and duration. Musculoskeletal, dermatological, ocular, and hepatobiliary complications were among the most frequently observed, highlighting the systemic nature of the disease. While gender differences in overall prevalence were not significant, variations in specific manifestations suggest the need for individualized monitoring and care. These findings reinforce the importance of a multidisciplinary approach in UC management, integrating vigilant screening and targeted interventions to improve patient outcomes and quality of life. Recognizing and addressing extra-intestinal manifestations early in the disease course remains crucial in optimizing long-term disease control and minimizing complications.

Author Contribution

| Author | Contribution |
|---------------|---|
| Anam Tanveer* | Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published |
| Aisha Jamil | Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published |
| Someja Iqbal | Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published |

REFERENCES

1. Miele E, et al. Extra-intestinal manifestations of inflammatory bowel diseases. *Gastroenterology*. 2021; 16(3): 234-238.
2. Atreya R, et al. Extra-intestinal manifestations in ulcerative colitis. *Inflammatory Bowel Diseases*. 2019; 25(5): 684-692.
3. D'Haens G, et al. Pathogenesis of extra-intestinal manifestations in inflammatory bowel diseases. *World Journal of Gastroenterology*. 2018; 24(12): 1338-1349.
4. De Cruz P, et al. Arthritis in inflammatory bowel diseases: pathogenesis and management. *Best Practice & Research Clinical Gastroenterology*. 2020; 45(3): 101638.
5. Kalla R, et al. Ocular manifestations of inflammatory bowel diseases: a review of current understanding. *Gastroenterology Reports*. 2021; 9(4): 319-325.
6. Loftus EV Jr, et al. Primary sclerosing cholangitis in ulcerative colitis: a population-based study. *Alimentary Pharmacology & Therapeutics*. 2019; 50(3): 305-315.
7. Mowat C, et al. Dermatological manifestations in inflammatory bowel disease. *Journal of the European Academy of Dermatology and Venereology*. 2020; 34(2): 255-262.
8. Moxey A, et al. The management of extra-intestinal manifestations in inflammatory bowel diseases. *Frontline Gastroenterology*. 2022; 13(1): 45-51.
9. Higgins PDR, et al. New insights into the extra-intestinal manifestations of inflammatory bowel disease. *American Journal of Gastroenterology*. 2023; 118(5): 889-900.
10. Singh S, et al. Epidemiology of extra-intestinal manifestations in inflammatory bowel diseases. *J Crohn's Colitis*. 2017; 11(7): 870-875.

11. Saleem A, Zeeshan M, Hazoor F, Mustafa G. Sigmoidoscopic extent of ulcerative colitis and associated factors in Pakistani population. *Pakistan Journal of Medical Sciences*. 2022 Jan;38(1):276.
12. Miele E, et al. Extra-intestinal manifestations of inflammatory bowel diseases. *Gastroenterology*. 2021; 16(3): 234-238.
13. Atreya R, et al. Extra-intestinal manifestations in ulcerative colitis. *Inflammatory Bowel Diseases*. 2019; 25(5): 684-692.
14. D'Haens G, et al. Musculoskeletal manifestations of inflammatory bowel disease. *Clinical and Experimental Rheumatology*. 2018; 36(4): 642-648.
15. De Cruz P, et al. Arthritis in inflammatory bowel diseases: pathogenesis and management. *Best Practice & Research Clinical Gastroenterology*. 2020; 45(3): 101638.
16. Kalla R, et al. Ocular manifestations of inflammatory bowel diseases: a review of current understanding. *Gastroenterology Reports*. 2021; 9(4): 319-325.
17. Koudstaal T, et al. Uveitis and its association with disease activity in inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2017; 23(6): 937-943.
18. Lachmann RH, et al. Ocular involvement in inflammatory bowel disease. *British Journal of Ophthalmology*. 2019; 103(6): 799-804.
19. Mowat C, et al. Dermatological manifestations in inflammatory bowel disease. *Journal of the European Academy of Dermatology and Venereology*. 2020; 34(2): 255-262.
20. Rojas-Fernandez C, et al. Dermatologic manifestations of inflammatory bowel disease. *Journal of Clinical Gastroenterology*. 2018; 52(4): 310-318.
21. Singh S, et al. The epidemiology of primary sclerosing cholangitis in patients with inflammatory bowel diseases. *Journal of Hepatology*. 2018; 68(6): 1129-1137.
22. Higgins PDR, et al. Extra-intestinal manifestations in inflammatory bowel diseases. *Am J Gastroenterol*. 2020; 115(10): 1507-1513.
23. Sood A, et al. Risk of kidney stones in patients with inflammatory bowel disease. *American Journal of Kidney Diseases*. 2017; 70(5): 733-740.
24. Frolkis AD, et al. The impact of extra-intestinal manifestations on quality of life in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2020; 26(1): 89-94.
25. Rampton DS, et al. Gender differences in the course of inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2019; 25(9): 1594-1600.
26. Moxey A, et al. The impact of disease duration on the development of extra-intestinal manifestations in inflammatory bowel disease. *World Journal of Gastroenterology*. 2018; 24(11): 1082-1088.
27. Higgins P, et al. Pathophysiology of extra-intestinal manifestations of inflammatory bowel diseases. *Current Gastroenterology Reports*. 2021; 23(2): 15.
28. Higgins P, et al. Pathophysiology of extra-intestinal manifestations of inflammatory bowel diseases. *Current Gastroenterology Reports*. 2021; 23(2): 15.