



A systematic review and meta-analysis of extra-intestinal manifestation of inflammatory bowel disease in the Eastern Mediterranean Region (EMRO) countries

Zahra Momayez Sanat, MD^{a,b}, Homayoon Vahedi, MD^b, Reza Malekzadeh, MD^b, Zeinab Fanni, MD^{a,*}

Background: Inflammatory bowel disease which is subgrouped mainly to ulcerative colitis and Crohn's disease is thought to be a multi-organ disease. Most organs can be involved in the disease course in addition to gastrointestinal tract involvement. In this systematic review we aimed to assess the prevalence of these manifestations in Eastern Mediterranean Regional Office (EMRO) countries.

Method: The present systematic review and meta-analysis study was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline. Joanna Briggs Institute (JBI) Critical Appraisal Checklist was admired for the quality evaluation of the included studies. For determining the heterogeneity, we used Cochran test and I^2 statistics.

Result: Finally, 12 studies were included in our study. Based on the results of our study the prevalence of arthritis in ulcerative colitis and Crohn's disease patients was 7.1% (95% CI: 2.6–18.2%) and 13.5% (95% CI: 2.6–47.3%), respectively. Prevalence of arthralgia in ulcerative colitis patients was 18.4% (95% CI: 14.3–23.3%). skin involvement prevalence was 9.9% (95% CI 4.7–19.6%) in inflammatory bowel disease (IBD) patients. ocular involvement prevalence was 7.2% (95% CI 17–25.8%) in IBD patients. PSC prevalence in ulcerative colitis and Crohn's disease patients was 3.5% (95% CI: 1.7–7.3%) and 2.7% (95% CI: 1.3–5.5%), respectively.

Conclusion: Based on the results of this study arthralgia and arthritis were the most common extra-intestinal manifestation of IBD followed by dermatologic and ocular involvements. This extra-intestinal manifestation can challenge the patients' management and identifying their pattern is important during the disease course.

Keywords: extra-intestinal manifestation, inflammatory bowel disease, meta-analysis, systematic review

Introduction

Inflammatory bowel disease (IBD) includes of two main subgroups of ulcerative colitis and Crohn's disease. This disease is now a global concern with significant prevalence and incidence worldwide^[1,2]. This disease has caused considerable burden globally along with significant individuals suffering from this condition^[3].

HIGHLIGHTS

- Inflammatory bowel disease which is subgrouped mainly to ulcerative colitis and Crohn's disease is thought to be a multi-organ disease.
- Finally 12 studies were included in our study.
- Based on the results of our study arthralgia and arthritis were the most common extra-intestinal manifestation of inflammatory bowel disease followed by dermatologic and ocular involvements.

^aTehran University of Medical Sciences and ^bDigestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Z.M.S., H.V. contributed equally to this work and share first authorship

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

*Corresponding author. Address: Tehran University of Medical Sciences, Tehran, Iran. Tel.: +988 241 5000; fax: + 988 241 5400. E-mails: zfanni.tums@gmail.com, zeinab_fanni@yahoo.com (Z. Fanni).

Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Annals of Medicine & Surgery (2024) 86:2892–2899

Received 25 August 2023; Accepted 17 November 2023

Published online 15 April 2024

<http://dx.doi.org/10.1097/MS9.0000000000001543>

Almost 6.8 million cases of IBD were identified in 2017 globally with the prevalence rate and death rate of 84.3 and 0.51, respectively^[4]. It is reported 2.5 million people in US and 1 million people in Europe suffering from IBD^[3]. Based on Global Burden of Disease (GBD) statements, North America and Caribbean were the regions with the highest and lowest prevalence of IBD, respectively^[4]. A study in the UK demonstrated that the prevalence of IBD has raised 33.8% between 2006 and 2016^[5].

IBD may occur as a result of the uncontrolled immune system response, which can originate from genetic or environmental determinants^[6]. Environmental factors and hereditary susceptibility are the most important cause of the IBD and its course. These two factors arouse the immune system to act overactive and impaired^[7,8]. Smoking, low physical activity, hygiene status,

Table 1
Basic characteristics of included studies

References	Country	Study period	Study design	Population	Sex		Sample size			Mean age			Mean age at diagnosis			Level of quality
					Male	Female	UC	CD	IBD	UC	CD	IBD	UC	CD	IBD	
Zobeiri et al. ^[20]	Iran	2014–2015	Retrospective study	IBD patients	77	79	153	3	156	NR	NR	31	NR	NR	NR	Medium
Yazdanbod et al. ^[21]	Iran	1998–2008	Retrospective study	patients with UC	44	61	105	—	—	33.5	—	—	—	—	—	Medium
Sidique et al. ^[22]	Kuwait	2005–2006	Cross-sectional	patients with UC	91	91	182	—	—	NR	NR	NR	28.5	—	—	High
Abdulla et al. ^[23]	Bahrain	1984–2014	Retrospective study	IBD patients	102	85	61	123	187	NR	NR	NR	28.3	24.1	27	Medium
Abduli-Baki et al. ^[24]	Lebanon	2000–2004	Retrospective study	IBD patients	164	87	142	100	251	NR	NR	NR	32.0	28.8	NR	Medium
Al-Shamali et al. ^[25]	Kuwait	1985–1999	Retrospective study	patients with UC	180	166	346	—	—	NR	NR	45	NR	NR	NR	High
Vahedi et al. ^[26]	Iran	2004–2007	Retrospective study	IBD patients	205	295	293	207	500	NR	NR	NR	37.1	33.8	NR	Medium
Ghanadi et al. ^[27]	Iran	2014–2015	Retrospective study	patients with UC	66	84	150	—	—	33.7	—	—	29.4	—	—	High
Al Fadda et al. ^[28]	Saudi Arabia	1970–2008	Retrospective study	IBD patients	152	160	115	197	312	23.8	28.4	25.5	NR	NR	NR	High
Masmadi Shirazi et al. ^[29]	Iran	2005–2007	Cross-sectional	IBD patients	106	94	183	17	200	37.2	32.8	NR	31.5	27	NR	High
Balati et al. ^[30]	Iran	2001–2013	Retrospective study	IBD patients	1120	1137	1914	318	2257	NR	NR	NR	33.8	32.9	NR	High
Alharbi et al. ^[31]	Saudi Arabia	2009–2013	Retrospective study	patients with UC	201	193	394	—	—	30.1	—	—	NR	—	—	Medium

IBD, inflammatory bowel disease; NR, not reported; UC, ulcerative colitis; CD, Crohn's disease.

surgeries, and antibiotic consumption are some environmental factors associated with IBD^[9]. Based on the epidemiological models, environmental factors can affect individuals based on a person's genetic characteristics, including age, sex, personality, and physical state, causing IBD susceptibility^[8,10].

Inflammatory bowel disease can involve other organs of body in addition to gastrointestinal tract which is defined as extra-intestinal manifestations (EIM)^[11,12]. The prevalence and incidence of EIMs varies between different organs. EIMs of IBD can happen before, within or after initiation of the disease and affect patients' management^[13]. It is estimated 25–40% of IBD patients experience EIMs and 25% of patients shows more than one EIMs^[14,15]. The pattern of EIMs of IBD can be accompanied by flaring the disease course or independent regarding the disease severity^[13]. Different organs are reported to be involved in as EIMs including dermatologic ocular musculoskeletal, hepatopancreatobiliary, pulmonary and renal systems^[16]. There are two distinct categories of EIM associated with IBD. Immune-related manifestations of IBD that are manifestations for reactive responses linked to the inflammatory activity in the intestines. They often share a common pathogenesis with the underlying intestinal disease like Arthritis, Erythema Nodosum (EN), Pyoderma Gangrenosum (PG), and Aphthous Stomatitis^[17]. Autoimmune disorders associated with IBD: as autoimmune conditions that are not directly tied to the activity of the intestines but result from an increased susceptibility to autoimmunity like Primary Biliary Cirrhosis, Alopecia Areata, and Thyroid Autoimmune Disease^[17]. These EIMs could be presented with a variety of symptoms, such as tenesmus, fever, exhaustion, diarrhoea, constipation, bloating, stomach discomfort, and inflammation of the liver, skin, eyes, and joints^[16].

Eastern Mediterranean Regional Office (EMRO) encompasses 22 countries which is one of the World Health Organization regional classification^[18]. The prevalence of EIMs of IBD was studied before in separate investigation however the was no comprehensive study to assess the all of them hence we aimed to conduct the present meta-analysis study to summarize the pattern of EIMs of IBD in this region.

Methods

Setting

The present study is a systematic review and meta-analysis aiming to identify the prevalence of EIMs of IBD in the EMRO countries. The study was conducted between 2021 and 2022 based on the Systematic Review and Meta-analysis (PRISMA) guideline^[19].

Search strategy

We searched four international databases such as Medline/PubMed, ProQuest, Scopus, and Web of knowledge from inception up to end of September, 2022. We included only papers with English language without any time limitation. The Selected keywords for international databases included: Epidemiology, prevalence, occurrence, risk factors, related factors, extra-intestinal manifestation, inflammatory bowel disease, ulcerative colitis, crohn's disease, Afghanistan, Bahrain, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Pakistan, Qatar, Saudi Arabia, Syria, United Arab Emirates, Djibouti, Egypt, Morocco,

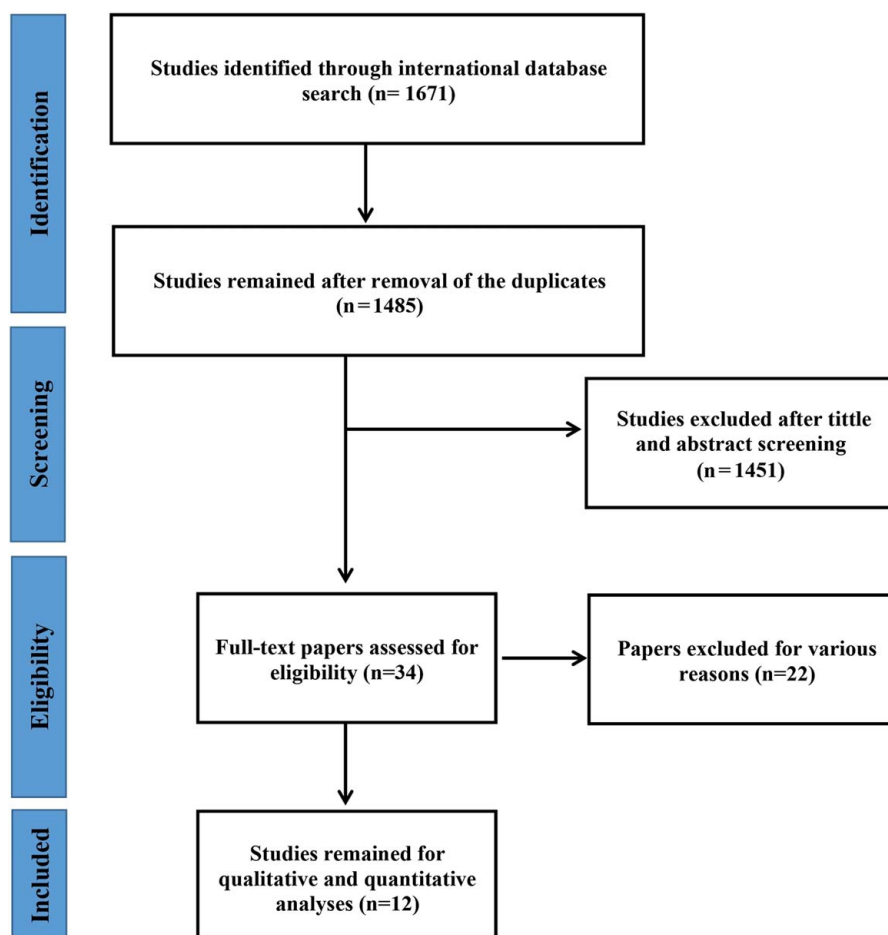


Figure 1. Flowchart of the included eligible studies in systematic review.

Palestine, Somalia, Sudan, Tunisia, Libya, and Yemen. The collected data entered to the EndNote X7 software, then, duplicate articles were automatically deleted. It is worthwhile to mention here that two researchers individually screened the articles based on title, abstract and full text.

Inclusion and exclusion criteria

Case-control, cross-section, and cohort studies assessing the IBD, Crohn's disease (CD), or ulcerative colitis (UC) individuals in the EMRO countries population with the following criteria were eligible to be included in our study: 1-IBD diagnosis should be confirmed using a comprehensive diagnostic approach. Patients underwent clinical evaluation, imaging studies, blood tests, and endoscopic procedures, including colonoscopy. Histopathological analysis of biopsies obtained during colonoscopy played a pivotal role in confirming the presence of IBD and differentiating it from other conditions, particularly in regions where conditions like tuberculosis are prevalent like EMRO. 2-at least one of the following outcomes was reported: The smoking rate in patients, family history, sites of involvement, risk factors of patients, incidence rate. 3-Studies in English 4- available full text. Studied which didn't fulfil the inclusion criteria got excluded. Two researchers

independently selected the studies, and any disagreements were solved by the third researcher.

Quality assessment

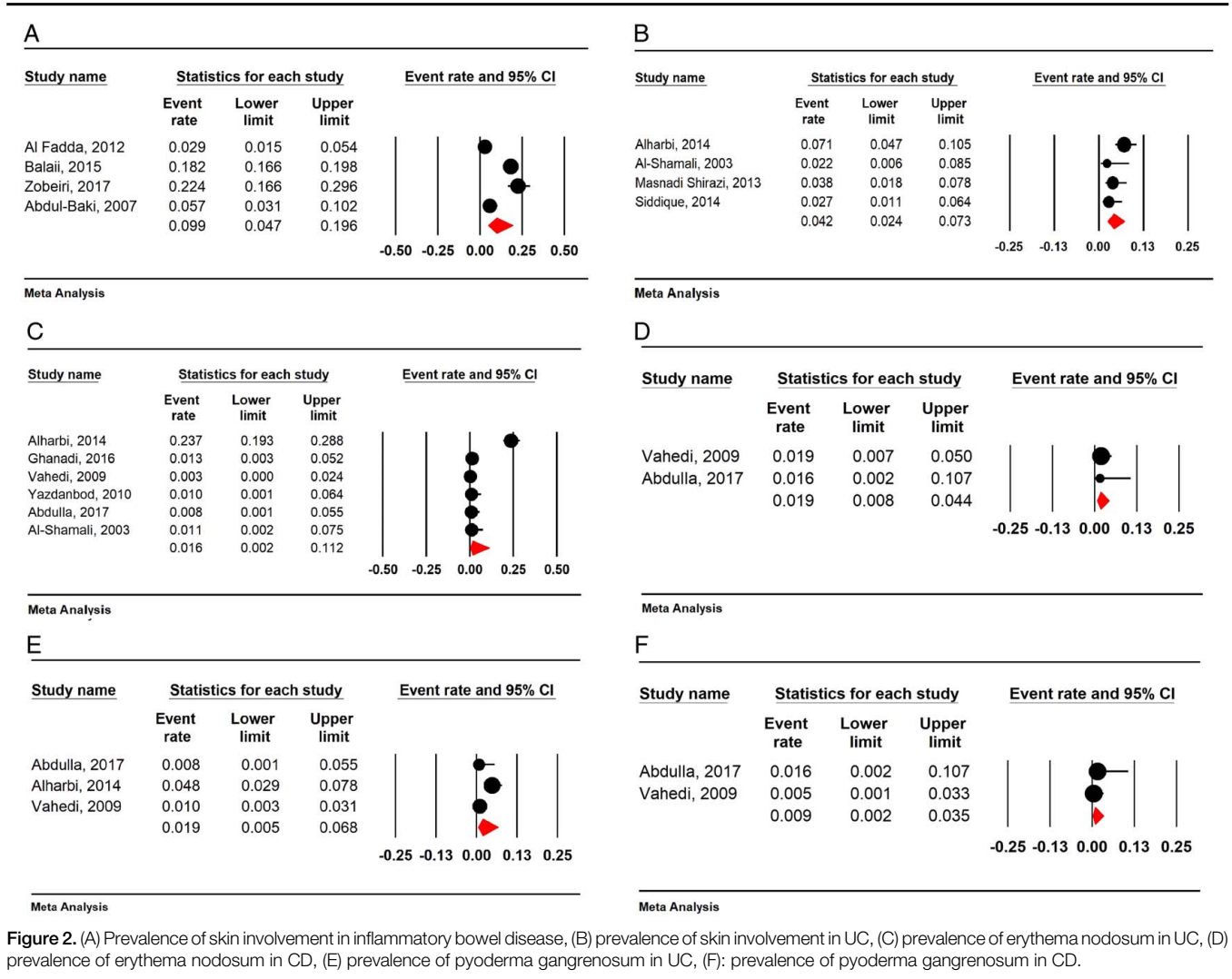
Two researchers performed the quality assessment of included studies using The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional, case-control, and cohort studies. Any disagreements were finalized by face-to-face consultation and the contribution of a third researcher. The JBI checklist scores of included studies are shown in Table 1.

Data extraction

Included papers were studied carefully by two researchers. The following outcomes were extracted: Name of the first author, year of publication, the place of study, duration of study, sample size of study, mean age of participants. The features of included studies are shown in Table 1.

Statistical analysis

Comprehensive meta-analysis (CMA) statistical software version 2 was admired for this study. Data were pooled when greater than or equal to three studies were available for a distinct outcome. Cochran's test (the significance level was



considered less than 0.1) and I^2 statistics (the significant level was considered more than 50%) were obtained to determine the heterogeneity of the results. Random-effect model was also used when heterogeneity was significant; otherwise fixed-effect model was applied.

Results

A total of 1671 studies were found in the initial search. After omitting the duplications 1485 Studies went for screening. Two researchers independently read the title, the abstract, and, when necessary, the full text of the articles. A total of 1416 Articles were deleted, and 69 papers went for full-text revision. Finally, 12 studies were included in our study based on inclusion criteria (Fig. 1).

Description of studies

The basic characteristic of included studies^[20–31] presented in Table 1. Based on the geographical location of 12 included studies, 6 studies conducted in Iran, 2 in Saudi Arabia, 2 in Kuwait,

one in Bahrain, one in UAE, and one in Lebanon. The summary characteristics of the studies are shown in Table 1.

Main results

Prevalence of skin involvement of IBD and UC patients was 9.9% (95% CI: 4.7–19.6%) and 4.2% (95% CI: 2.4–7.3%), respectively. prevalence of erythema nodosum in UC and CD was 1.6% (95% CI: 0.2–11.2%) and 1.9% (95% CI: 0.8–4.4%), respectively. prevalence of pyoderma gangrenosum in UC and CD was 1.9% (95% CI: 0.6–1.8%) and 0.9% (95% CI: 0.2–3.5%), respectively (Fig. 2).

Prevalence of arthritis in UC and CD patients was 7.1% (95% CI: 2.6–18.2%) and 13.5% (95% CI: 2.6–47.3%), respectively. Prevalence of arthralgia in UC patients was 18.4% (95% CI: 14.3–23.3%) (Fig. 3).

Ocular involvement prevalence was 7.2% (95% CI 17–25.8%) in IBD patients. in UC patients 2.5% (95% CI: 0.8–7.5%) had ocular lesions. PSC prevalence in UC and CD patients was 3.5% (95% CI: 1.7–7.3%) and 2.7% (95% CI: 1.3–5.5%), respectively. PSC prevalence in IBD patients was 1% (95% CI: 0.00–4.9%) (Fig. 4).

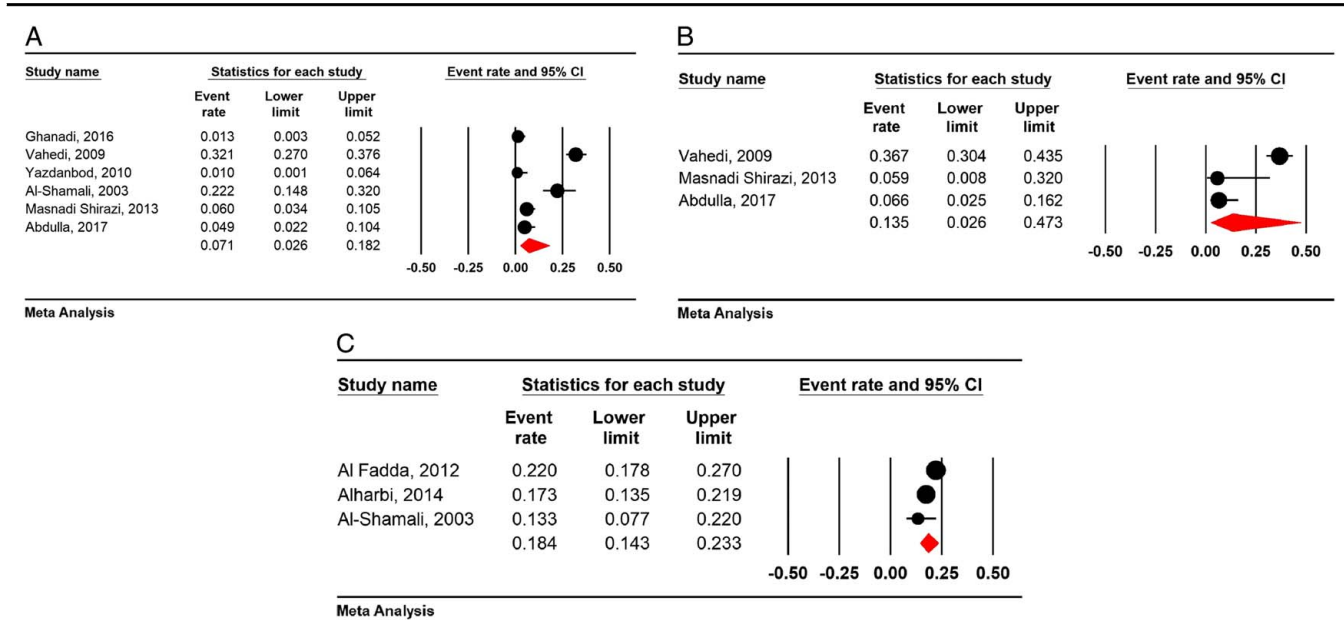


Figure 3. (A) Prevalence of arthritis in UC, (B) prevalence of arthritis in CD, (C) prevalence of arthralgia in UC.

Discussion

IBD is a multisystem disease not only affecting gastrointestinal tract but other organs can be involved. Extra-intestinal manifestation of BD can occur in different organs including dermatologic ocular musculoskeletal, hepatopancreatobiliary, pulmonary renal, systems. The management of IBD patients with extra-intestinal manifestation is more challenging^[16]. The present study we aimed to discuss the extra-intestinal manifestation of IBD in EMRO countries population.

The most common presentation of EIMs of IBD is observed in musculoskeletal system^[14,15,32]. In our study EIMs of IBD are mostly observed as arthralgia and arthritis. The prevalence of arthritis was more common in CD compared to UC. Previous studies reported prevalence of arthralgia 40–50% in IBD population while the prevalence of arthritis is reported 15–20% and 10% in CD and UC patients, respectively^[33]. Arthritis occurs both in men and women equally and is more common in patients with colon involvement compared to small intestine involvement^[13,34]. Arthritis in IBD patients can involve both peripheral and axial joints, small and large joints^[16]. Peripheral arthritis usually affects large joints and is often asymmetric^[13,16]. The joint involvement is usually non erosive and seronegative in IBD patient^[16].

Additionally, other parts of the world also conducted several studies to assess the EIM of IBD. For example, a comprehensive IBD cohort study based in Switzerland, with a specific emphasis on extra-intestinal manifestations, revealed that as many as 25% of individuals with IBD who experience these manifestations are affected by multiple EIMs^[35].

Based on the results of our study the prevalence of skin involvement in IBD patients is 9.9% in EMRO countries. In other studies 2–34% of IBD patients manifested dermatologic involvement^[36]. A wide range of skin manifestations have been reported Erythema nodosum, pyoderma gangrenosum, oral aphthous stomatitis, psoriasis, and Sweet syndrome^[36]. In our

study Erythema nodosum was more common in CD patients while Pyoderma gangrenosum was more common in UC patients. In a prospective study by Yüksel *et al.*^[37] 7.4% and 2.3% of IBD patients manifested dermatological features as Erythema nodosum, and pyoderma gangrenosum, respectively.

One of the most significant EIMs of IBD is PSC which is defined as chronic inflammation and fibrosis of intra and extra hepatic bile duct due to unknown aetiology^[38]. PSC is strongly associated with UC and less common CD. It is estimated coexistence of UC and CD in PSC patients is 75% and 5–10%, respectively. More over the prevalence of PSC in UC and CD patients is reported 5% and 2%, respectively^[16]. PSC is more common in adults patient compared to paediatrics^[39]. In our study prevalence of PSC was more common in UC compared to CD which was consistent with other studies.

Ocular involvement is the third major organ which is for EIMs after articular and akin involvement^[40]. Ocular manifestation can occur in a wide clinical range as scleritis, Episcleritis, papillitis, retinal vasculitis and corneal infiltrates, myositis anterior uveitis, and optic neuritis^[34,41]. Based on the results of our study 7.2% of IBD patients showed ocular manifestations. Other studies reported 0.5–3% of IBD patients showed ocular manifestation^[41]. The prevalence of ocular manifestation is higher in patients with colon involvement compared to small intestine involvement^[16].

Based on the results of our study arthralgia and arthritis were the most common extra-intestinal manifestation of IBD followed by dermatologic and ocular involvements. These extra-intestinal manifestation can challenge the patients' management and identifying their pattern is important during the disease course.

In the end, most individuals with IBD have active, healthy lives, with flare-ups and remissions occurring on a cyclical basis. A key component of symptom management is lifestyle adjustments in conjunction with effective therapy. Achieving these goals requires careful screening, early detection of EIMs, and rapid intervention to minimize morbidity and improve quality of life^[34]. The

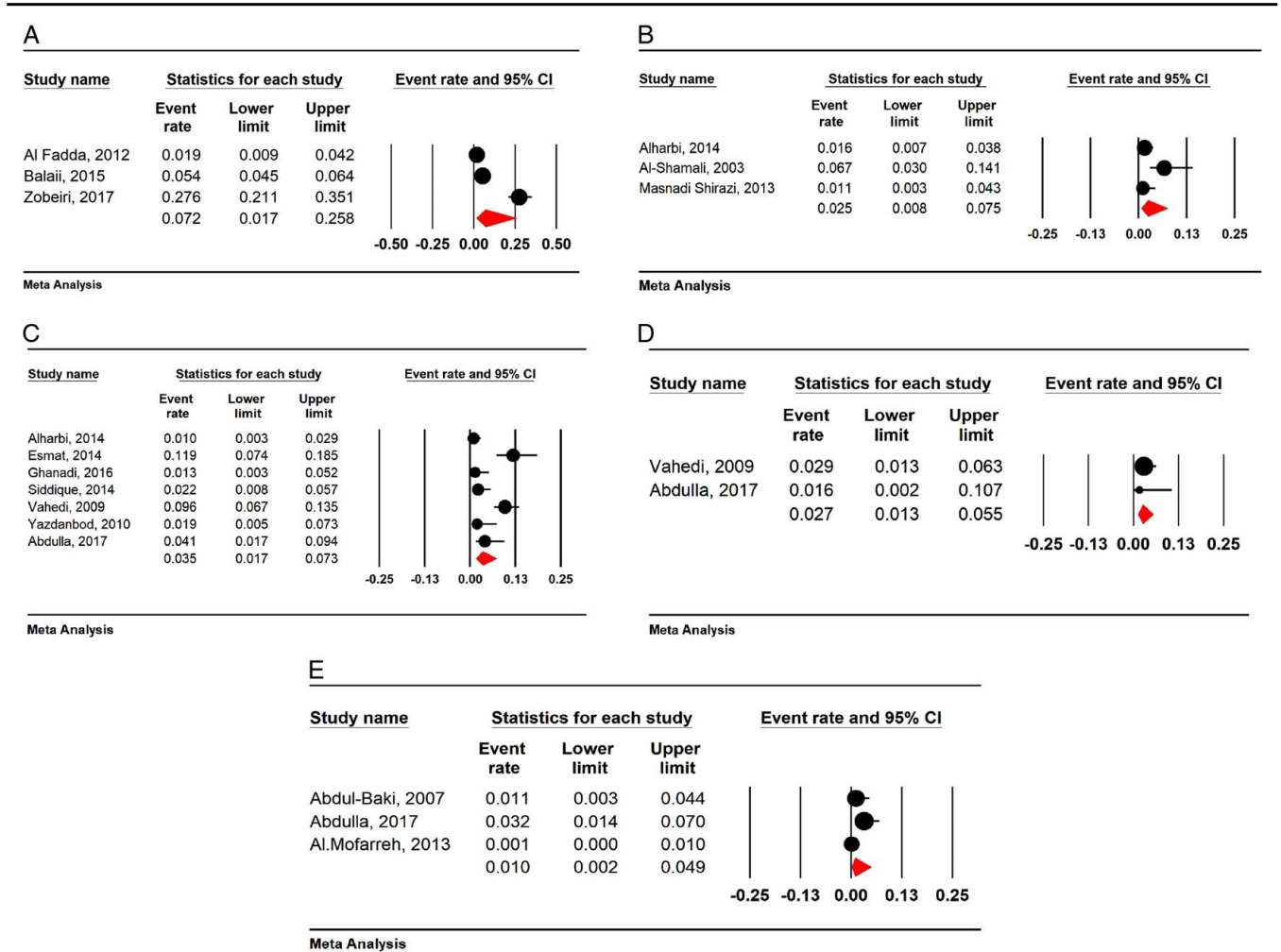


Figure 4. (A) Ocular manifestation prevalence in inflammatory bowel disease (IBD), (B) ocular manifestation prevalence in UC, (C) prevalence of PSC in UC, (D) prevalence of PSC in CD, (E) prevalence of PSC in IBD.

treatment of EIMs of IBD necessitates a multidisciplinary approach, combining medical intervention with lifestyle modifications. The resolution of EIMs often corresponds with the successful management of intestinal-IBD activity. However, EIMs that are independent of IBD activity require specific treatments aimed at improving the patient’s quality of life and reducing morbidity and mortality^[34]. For musculoskeletal EIMs associated with IBD, a comprehensive approach includes physiotherapy and the use of analgesics and anti-inflammatory medications, such as nonsteroidal anti-inflammatory drugs and systemic corticosteroids. Cutaneous manifestations like pyoderma gangrenosum benefit from topical corticosteroid therapy, coupled with wound care to promote healing. Ocular manifestations, such as scleritis and uveitis, typically require treatment with topical corticosteroids to manage inflammation and discomfort^[16,34].

Limitation

During the course of conducting this meta-analysis, several limitations have come to our attention. First, we encountered a shortage of suitable articles from certain countries in the

EMRO. Secondly, a subset of the articles we included in our analysis failed to comprehensively discuss all the EIMs of IBD specific to their respective regions. Lastly, a noteworthy limitation is the absence of information regarding the timing of the patients’ diagnoses.

Conclusion

In conclusion, this systematic review and meta-analysis have provided valuable insights into the prevalence and patterns of EIMs in IBD within the EMRO. Our comprehensive analysis of the available data revealed that EIMs are not uncommon among IBD patients in this region, with varying prevalence rates among different EMRO countries. We observed that EIMs significantly impact the clinical course and quality of life of IBD patients, highlighting the need for heightened awareness and effective management strategies. Our findings also underscore the importance of early detection and a multidisciplinary approach to care, involving gastroenterologists, rheumatologists, dermatologists, and other specialists. Collaboration and knowledge-sharing among healthcare professionals can aid in the prompt

identification and management of EIMs in IBD, thereby improving patient outcomes.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agreed to publish.

Sources of funding

There was no funding support for this work.

Author contribution

Z.M.S., R.M. and Z.F. contributed to the conception and design of the study. H.V., R.M. and Z.M.S. drafted the manuscript, H.V. and Z.F. analyzed and examined the data. Z.M.S. and H.V. participated in the literature search, quality assessment, and writing work. Z.M.S., R.M. and Z.F. participated in literature screening and data extraction. All the authors have approved the final version of the manuscript.

Conflicts of interest disclosure

All authors declare that they have no competing interest.

Research registration unique identifying number (UIN)

Due to the finalization of the manuscript, it is not possible to register it on the PROSPERO website. According to the rules of PROSPERO, submission is not allowed for 40 days after registration in the system. Therefore, we do not have the conditions to register on the PROSPERO website.

Guarantor

Zeinab Fanni Tehran University of Medical Sciences, Tehran, Iran E-mail: zfanni.tums@gmail.com, zeinab_fanni@yahoo.com.

Data availability statement

The data can be made available upon request to the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

- [1] Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;390:2769–78.
- [2] Olfatifar M, Zali MR, Pourhoseingholi MA, *et al.* The emerging epidemic of inflammatory bowel disease in Asia and Iran by 2035: a modeling study. *BMC Gastroenterol* 2021;21:204.
- [3] Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015;12:720–7.
- [4] GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020;5: 17–30.
- [5] Freeman K, Ryan R, Parsons N, *et al.* The incidence and prevalence of inflammatory bowel disease in UK primary care: a retrospective cohort study of the IQVIA Medical Research Database. *BMC Gastroenterol* 2021;21:1–7.
- [6] Sairenji T, Collins KL, Evans DV. An update on inflammatory bowel disease. *Prim Care: Clin Office Pract* 2017;44:673–92.
- [7] Loddo I, Romano C. Inflammatory bowel disease: genetics, epigenetics, and pathogenesis. *Front Immunol* 2015;6:551.
- [8] Kaser A, Zeissig S, Blumberg RS. Genes and environment: how will our concepts on the pathophysiology of IBD develop in the future? *Digest Dis* 2010;28:395–405.
- [9] Piovani D, Danese S, Peyrin-Biroulet L, *et al.* Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology* 2019;157:647–59.e4.
- [10] Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Hepatol* 2011;7:235.
- [11] Garber A, Regueiro M. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, etiopathogenesis, and management. *Curr Gastroenterol Rep* 2019;21:31.
- [12] Adam H, Alqassas M, Saadah OI, *et al.* Extraintestinal manifestations of inflammatory bowel disease in middle eastern patients. *J Epidemiol Glob Health* 2020;10:298–303.
- [13] Rogler G, Singh A, Kavanaugh A, *et al.* Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. *Gastroenterology* 2021;161: 1118–32.
- [14] Bernstein CN, Blanchard JF, Rawsthorne P, *et al.* The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001;96:1116–22.
- [15] Isaacs KL. How prevalent are extraintestinal manifestations at the initial diagnosis of IBD? *Inflamm Bowel Dis* 2008;14(suppl 2): S198–9.
- [16] Vavricka SR, Schoepfer A, Scharl M, *et al.* Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:1982–92.
- [17] Sange AH, Srinivas N, Sarnaik MK, *et al.* Extra-intestinal manifestations of inflammatory bowel disease. *Cureus* 2021;13:e17187.
- [18] World Health Organization. Regional Office for the Eastern Mediterranean 2023. <https://www.emro.who.int/countries.html>
- [19] Moher D, Liberati A, Tetzlaff J, *et al.* Linee guida per il reporting di revisioni sistematiche e meta-analisi: il PRISMA Statement. *PLoS Med* 2009;6:e1000097.
- [20] Zobeiri M, Bashiri H, Askari L, *et al.* Epidemiologic characteristics of patients with inflammatory bowel disease in Kermanshah, Iran. *Middle East J Digest Dis* 2017;9:164–9.
- [21] Yazdanbod A, Farzaneh E, Pourfarzi F, *et al.* Epidemiologic profile and clinical characteristics of ulcerative colitis in northwest of Iran: a 10-year review. *Trop Gastroenterol* 2011;31:308–11.
- [22] Siddique I, Alazmi W, Al-Ali J, *et al.* Demography and clinical course of ulcerative colitis in Arabs - a study based on the Montreal classification. *Scand J Gastroenterol* 2014;49:1432–40.
- [23] Abdulla M, Al Saeed M, Fardan RH, *et al.* Inflammatory bowel disease in Bahrain: single-center experience. *Clin Exp Gastroenterol* 2017;10: 133–45.
- [24] Abdul-Baki H, ElHajj I, El-Zahabi LM, *et al.* Clinical epidemiology of inflammatory bowel disease in Lebanon. *Inflamm Bowel Dis* 2007;13: 475–80.
- [25] Al-Shamali MA, Kalaoui M, Patty I, *et al.* Ulcerative colitis in Kuwait: a review of 90 cases. *Digestion* 2003;67:218–24.
- [26] Vahedi H, Merat S, Momtahan S, *et al.* Epidemiologic characteristics of 500 patients with inflammatory bowel disease in Iran studied from 2004 through 2007. *Arch Iran Med* 2009;12:454–60.
- [27] Ghanadi K, Valizadeh J, Hasanvand A. Epidemiological and clinical aspects of ulcerative colitis in west of Iran: a cross sectional study. *SpringerPlus* 2016;5:1588.
- [28] Fadda MA, Peedikayil MC, Kagevi I, *et al.* Inflammatory bowel disease in Saudi Arabia: a hospital-based clinical study of 312 patients. *Ann Saudi Med* 2012;32:276–82.

- [29] Shirazi KM, Somi MH, Bafandeh Y, *et al.* Epidemiological and clinical characteristics of inflammatory bowel disease in patients from north-western Iran. *Middle East J Digest Dis* 2013;5:86–92.
- [30] Balaii H, Asadzadeh Aghdaei H, Farnood A, *et al.* Time trend analysis and demographic features of inflammatory bowel disease in Tehran. *Gastroenterol Hepatol From Bed To Bench* 2015;8:253–61.
- [31] Alharbi OR, Azzam NA, Almalki AS, *et al.* Clinical epidemiology of ulcerative colitis in Arabs based on the Montréal classification. *World J Gastroenterol* 2014;20:17525–31.
- [32] Aghazadeh R, Zali MR, Bahari A, *et al.* Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol* 2005;20:1691–5.
- [33] Orchard TR. Management of arthritis in patients with inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2012;8:327–9.
- [34] Malik TF, Aurelio DM. Extraintestinal Manifestations of Inflammatory Bowel Disease 2023 In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. <https://www.ncbi.nlm.nih.gov/books/NBK568797/>
- [35] Vavricka SR, Rogler G, Gantenbein C, *et al.* Chronological order of appearance of extraintestinal manifestations relative to the time of IBD diagnosis in the Swiss Inflammatory Bowel Disease Cohort. *Inflamm Bowel Dis* 2015;21:1794–800.
- [36] Tavela Veloso F. Review article: skin complications associated with inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;20(suppl 4): 50–3.
- [37] Yüksel I, Başar O, Ataseven H, *et al.* Mucocutaneous manifestations in inflammatory bowel disease. *Inflamm Bowel Dis* 2009;15: 546–50.
- [38] Lee YM, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med* 1995;332:924–33.
- [39] Kaplan GG, Laupland KB, Butzner D, *et al.* The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. *Am J Gastroenterol* 2007;102:1042–9.
- [40] Taleban S, Li D, Targan SR, *et al.* Ocular manifestations in inflammatory bowel disease are associated with other extra-intestinal manifestations, gender, and genes implicated in other immune-related traits. *J Crohns Colitis* 2016;10:43–9.
- [41] Petrelli EA, McKinley M, Troncale FJ. Ocular manifestations of inflammatory bowel disease. *Ann Ophthalmol* 1982;14:356–60.