Review Article

The Prevalence of Migraine in Inflammatory Bowel Disease, a Systematic Review and Meta-Analysis

Abstract

Background: Patients with inflammatory bowel disease (IBD) suffer from a wide range of comorbidities such as migraine. In studies, the prevalence of migraine in cases with IBD was reported differently. The goal of this systematic review and meta-analysis was to estimate the pooled prevalence of migraine in IBD cases. **Methods:** Two researchers independently and systematically searched PubMed, Scopus, EMBASE, Web of Science, and google scholar. They also searched the gray literature including references of the included studies and conference abstracts which were published up to May 2021. Cross-sectional studies were included. **Results:** The literature search revealed 840 articles, and after deleting duplicates, 650 remained. For the meta-analysis, 10 studies were included. Totally, 62,554 patients were evaluated. The pooled prevalence of migraine in patients with IBD was 19% (95% CI: 15–22%). The pooled prevalence of migraine in ulcerative colitis (UC) was 10% (95% CI: 4–15%) (I^2 = 99.8%, P < 0.001). The pooled prevalence of migraine in the Crohn's disease (CD) group was 24% (95% CI: 17–30%) (I^2 = 98.8%, P < 0.001). The pooled odds of developing migraine in IBD cases was 1.51 (95% CI: 1–2.27) (I^2 = 90.8%, P < 0.001). **Conclusions:** The result of this systematic review and meta-analysis showed that the pooled prevalence of migraine in patients with IBD was 19% (95% CI: 15–22%).

Keywords: *Inflammatory bowel disease, migraine disorders, prevalence*

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Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a complex chronic disease affecting primarily the gastrointestinal tract along with other organs.[1,2] The prevalence of IBD is reported as 0.4% in developed countries.[1]

It is well known that IBD is associated with a number of extra-intestinal diseases. Some of them are complications of the disease process such as venous thromboembolism (VTE), whereas others are considered as extra-gastrointestinal (GI) manifestations.[3]

Extra-GI manifestations include articular, cutaneous, neurological, and ocular involvement with prevalence of 40%.[4,5]

Previous studies demonstrated that the prevalence of neurological manifestations in IBD cases ranges between 25 and 37.5%.[6-8]

Migraine is a chronic disorder affecting women more than men and is the first cause of disability under 50.[9] Its origin is not clear as brain–gut interactions are considered as pathogenesis of the migraine in patients with IBD[2] as well as side effects of immunosuppressive agents.

Previous studies demonstrate that the prevalence of migraine in patients with IBD is more than the general population and the odds are increased by 2.6-fold.[10,11]

As the prevalence of migraine in cases with IBD is reported variously, we designed this systematic review and meta-analysis to estimate the pooled prevalence of migraine in IBD cases.

Methods

Literature search

Two researchers independently and systematically searched PubMed, Scopus, EMBASE, Web of Science, and google scholar. They also searched the gray literature including references of the included studies and conference abstracts which were published up to May 2021.

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Inclusion criteria

We included cross-sectional studies which had reported the number of patients with IBD who had migraine diagnosis.

Exclusion criteria

Letters to the editor, case-control, case reports, and cross-sectional studies which had no clear data regarding the prevalence of migraine in enrolled cases were excluded.

Data search and extraction

- The search strategy included the MeSH and text words as ("Migraine Disorder" OR (Migraine AND Disorder) OR "Migraine Disorders" OR (Migraine AND Disorders) OR "Migraine" OR "Migraines" OR "Migraine Headache" OR (Migraine AND Headache) OR "Migraine Headaches" OR (Migraine AND Headache)) AND ("Inflammatory Bowel Disease" OR "Inflammatory Bowel Diseases" OR (Inflammatory AND Bowel Disease) OR (Inflammatory AND Bowel Diseases) OR "Idiopathic Proctocolitis" OR (Idiopathic AND Proctocolitis) OR "Ulcerative Colitis" OR (Ulcerative AND Colitis) OR "Colitis Gravis" OR (Colitis AND Gravis) OR "Crohn's Enteritis" OR (Crohn's AND Enteritis) OR "Regional Enteritis" OR (Regional AND Enteritis) OR "Crohn's Disease" OR (Crohn's AND Disease) OR "Regional Ileitis" OR (Ileitis AND Regional) OR "Terminal Ileitis" OR (Terminal AND Ileitis) OR "Ileocolitis" OR "Granulomatous Colitis" OR (Granulomatous AND Colitis) OR "Granulomatous Enteritis" OR (Granulomatous AND Enteritis)). Two independent researchers independently evaluated the articles.

We extracted data regarding the total number of participants, first author, publication year, the country of origin, mean age, sex frequency, and number with migraine.

Risk of bias assessment

We evaluated the risk of potential bias using the NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (adapted for cross-sectional studies).[12,13] It is used for evaluating the quality of non-randomized studies including three sections (selection, comparability, and outcome). It has totally seven questions. The maximum total score could be 10 [Tables 2 & 3].

Statistical analysis

All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA).

To determine heterogeneity, inconsistency (I^2) was calculated.

As the heterogeneity between results of included studies was more than 50%, we used the random effects model. Pooled prevalence of migraine in IBD cases as well as UC and Crohn's subgroups is reported with 95% CI.

Results

The literature search revealed 840 articles, and after deleting duplicates, 650 remained. For the meta-analysis, 10 studies were included [Figure 1].

Totally, 62,554 patients were evaluated. The mean age ranged from 17 to 53 years [Table 1].

The pooled prevalence of migraine in patients with IBD was 19% (95% CI: 15–22%) (I^2 = 99.2%, P < 0.001) [Figure 2].

The pooled prevalence of migraine in controls was 6% (95% CI: 4–8%) (I2: 99.9%, P < 0.001) [Figure 3].

The pooled prevalence of migraine in UC was 10% (95% CI: 4–15%) (I^2 = 99.8%, P < 0.001) [Figure 4].

The pooled prevalence of migraine in CD was 24% (95% CI: 17–30%) (I^2 = 98.8%, P < 0.001) [Figure 5].

The pooled odds of developing migraine in IBD cases was 1.51 (95% CI: 1–2.27) (I^2 = 90.8%, P < 0.001) [Figure 6].

Discussion

To our knowledge, this is the first systematic review and meta-analysis evaluating the prevalence of migraine in patients with IBD. The results of this study showed that the pooled prevalence of migraine in IBD cases is 19%, whereas the prevalence is higher in CD cases than UC ones (24% vs 10%). The results also show that the odds of developing migraine are significantly higher in IBD cases when compared with controls (1.5-fold).

In a study in Iran, Cheraghi *et al*.[8] reported the prevalence of migraine in 21.3% of IBD cases compared to 8.8% of controls. In another study which was conducted by Dimitrova *et al*.,[11] the prevalence of migraine was reported as 14% in IBD cases and 6% in controls.

Ghersin *et al*.[17] assessed 295 UC and 595 CD cases and reported no association between migraine and IBD. In their study, none of the UC cases and only 8 CD cases had migraine.

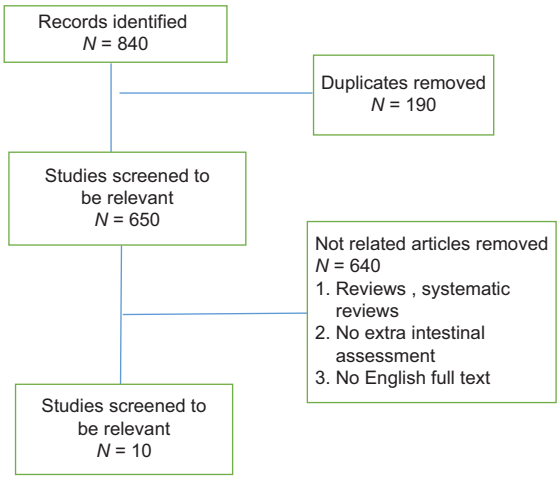

Figure 1: Flow diagram of including studies

Table 1: Basic characteristics of the included studies

Author	Country	Year of publication	Year of study	Type of article	Demographic features				Number of IBD patients			Number of migraine patients			IBD duration	Controls data				
					Age	Number										Demographic				Number of Migraine in control
						F	M	T	CD	UC	Total	In CD	In UC	In Total		Age	F	M	T	
J. Tajti Jr	Hungary	2019	2005-2016	Retrospective abstract	NA	-	-	-	-	75	75	-	-	8	-	-	-	-	-	-
Leitão *et al.*[14]	Brazil	2020	2015-2016	cross-sectional, prospective	43 (1)	83	72	155	75	80	155	30	23	53		46 (2)	35	66	101	21
Bähler[15]	Switzerland	2017	2014	cross-sectional	56 (28)	2684	2107	4791	-	-	4791	-	-	105	-	44	575943	538695	1114638	12261
Anadol Kelleci *et al.*[16]	Turkey	2016	2012	cross-sectional	35 (12)	26	25	51	51	-	51	35	-	9	29.17 (10.24)	35 (9)	27	24	51	21
Card *et al.*[3]	United Kingdom	2016	1987-2011	cohort	47.2	29814	26283	56097	18204	27108	56097	1430	1892	4380	-	47.2	149030	131352	280,382	19376
Dimitrova *et al.*[11]	United States	2013	2010-2011	Prospective	36.5	58	53	111	-	-	111	-	-	25	-	47.8	109	69	178	25
Ford *et al.*[10]	United States	2009	2006	Prospective	40.3 (14.9)	77	23	100	66	27	100	24	4	28	12.11 (10.19)	-	-	-	-	-
Ghersin *et al.*[17]	Israel	2019	2004-2016	cohort	17.1	318	573	891	595	296	891	8	0	8	-	-	-	-	1,141,841	37,576
Cheraghi *et al.*[8]	Iran	2016	2014	Cross-sectional	35	33	47	80	18	62	80	-	-	17	-	34.69	36	44	80	7
Moisset *et al.*[2]	France	2017	2014-2015	Cohort	40.1 (1)	113	90	203	129	73	203	-	-	83	10.5 (0.7)	-	-	-	-	-

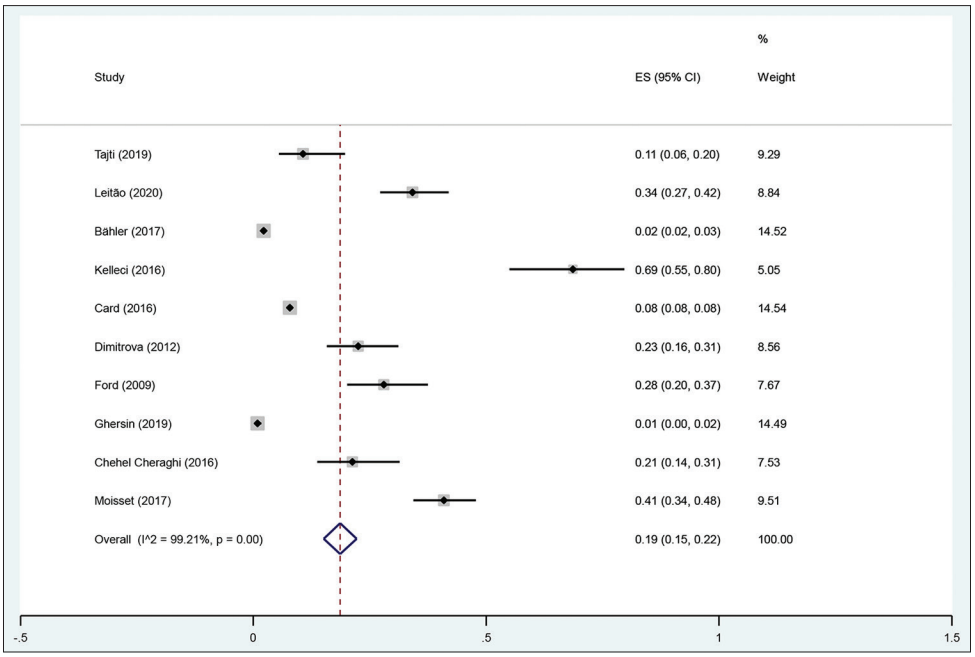

Figure 2: The pooled prevalence of migraine in patients with IBD

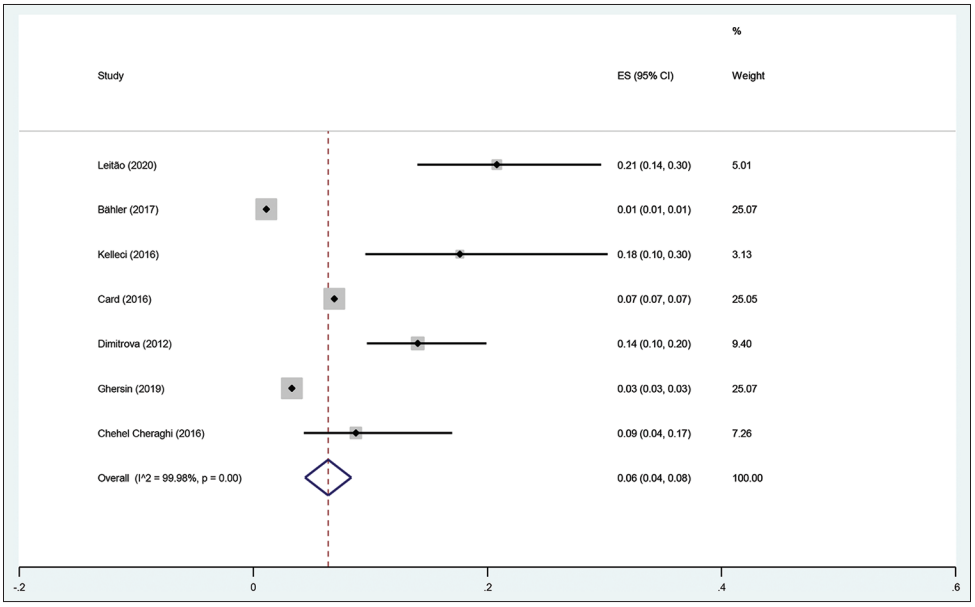

Figure 3: The pooled prevalence of migraine in controls

Table 2: Quality assessment of included studies

Name of the author	Questions								Total score
	Selection questions				Comparability questions	Outcome questions			
	Q1	Q2	Q3	Q4	Q1	Q1	Q2	Q3	
Timothy R. Card	A*	B*	D	A*	A*	D	A*	A*	6
Sutapa Ford	B*	C	B*	A*	C	C	A*	A*	5
Itai Ghersin	A*	A*	D	A*	C	D	A*	A*	5

In a cross-sectional study which was conducted by Ford *et al*.,[10] the prevalence of migraine in IBD was 30% and the prevalence was higher in CD cases than in UC ones (36 vs 14%).

Peripheral and central nervous systems could be affected in patients with IBD.[18,19]

Migraine is a disabling disease affecting women more than men which interferes with daily activity and sexual life and

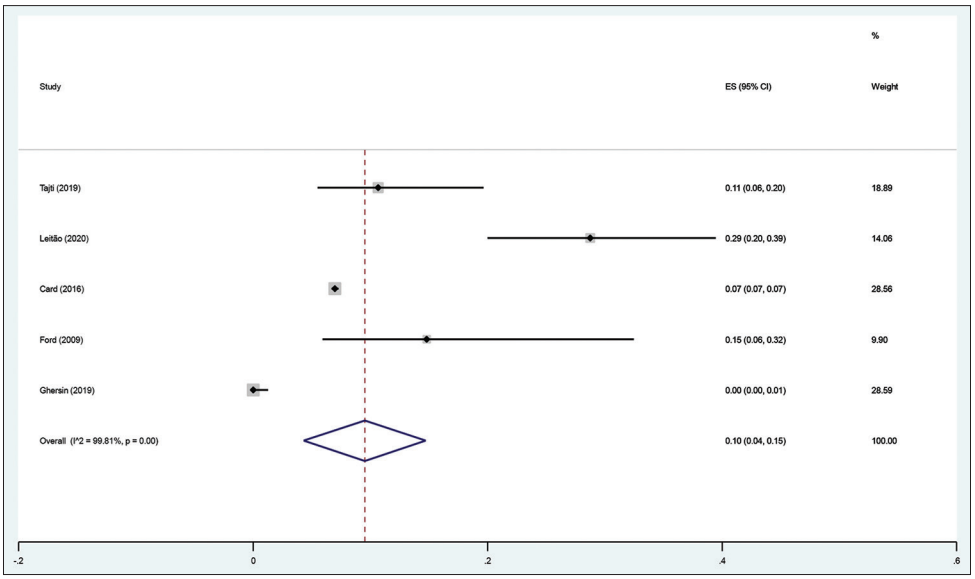

Figure 4: The pooled prevalence of migraine in UC

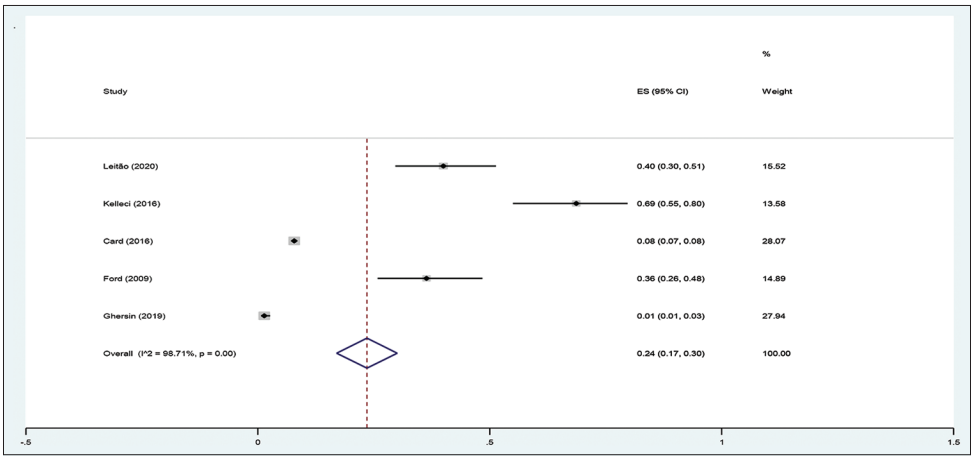

Figure 5: The pooled prevalence of migraine in CD

Table 3: Quality assessment of cross-sectional studies

Name of the author	Questions							Total score
	Selection				Comparability	Outcome		
	Q1	Q2	Q3	Q4	Q1	Q1	Q2	
Antônio M. F. Leitão	A*	A*	C	A**	-	C*	A*	6
Caroline Bähler	A*	A*	C	C	-	B**	A*	5
Ulker Anadol Kelleci	B*	A*	C	A**	B*	C*	A*	7
Alexandra K. Dimitrova	A*	A*	C	A**	-	C*	A*	6
Somaye Chehel Cheraghi	B*	A*	C	A**	A*	C*	A*	7
X. Moisset	A*	A*	C	A**	-	C*	A*	6

impairs the quality of sleep and life.[20-22] Genetics plays an important role in developing migraine when there is a relationship between auto-immune disease and incidence of migraine, such as rheumatoid arthritis (RA), systemic lupus erythematosus, and multiple sclerosis.[23-26] In a study which was conducted by AbdElaty ElSonbaty, the prevalence of migraine in patients with RA was estimated as 28%, and in a recent systematic review and meta-analysis, the pooled prevalence of migraine in patients with multiple sclerosis was estimated as 31%.[25,26]

The exact cause of migraine is unclear as neuronal and vascular mechanisms are involved.

The link between migraine and IBD could be clarified by the presence of systemic inflammation leading to neurogenic inflammation presenting with migraine.[27]

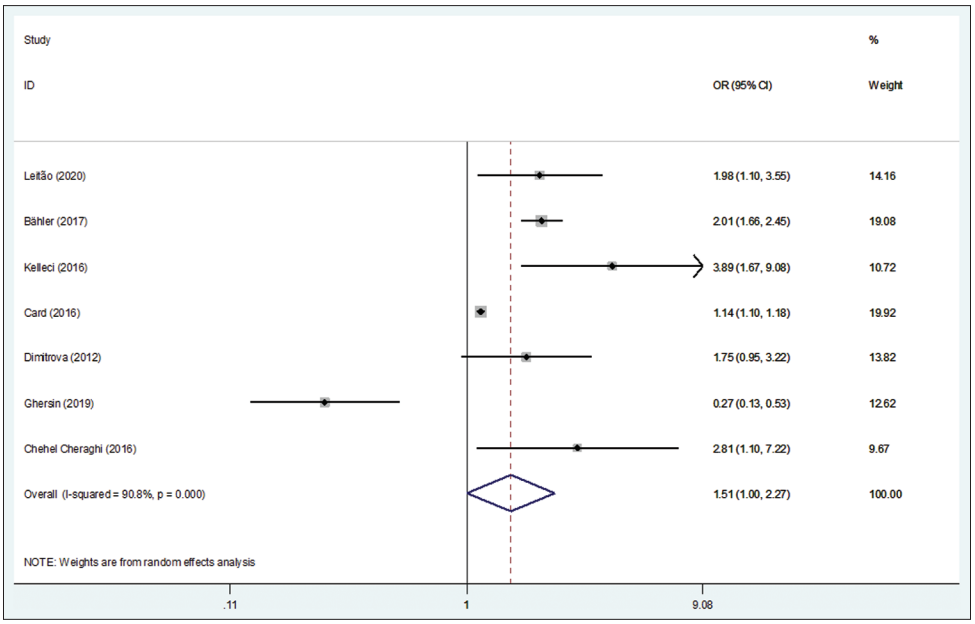

Figure 6: The pooled odds of developing migraine in IBD cases

Nowadays, the brain-gut axis is considered in the pathogenesis of some diseases. One of them is the serotonergic system.[28] The level of serotonin is low between attacks and increases during migraine attacks, which shows a relationship between the low serotonin level and migraine incidence.[29] It has been shown that in patients with UC, expression of the serotonin transporter in the gut epithelium is decreased and the level of serotonin is less than normal in the colon.[30] Low serotonin levels could be the link between migraine and IBD.

Higher serum levels of cytokines in IBD cases than controls could flare headache. Moisset *et al*.[2] showed that migraine is not associated with IBD clinical activity. They found that inflammatory activity is sufficient for migraine activity when there are no intestinal manifestations. The literature shows that C-reactive protein (CRP), matrix metallopeptidase 9 (MMP-9), cytokines, adhesion molecules, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and inducible nitric oxide synthase (iNOS) have roles in developing migraine headache.[31-33]

This systematic review and meta-analysis has some strength. It is the first study. Second, we estimated pooled prevalence in CD and UC separately.

Conclusions

The result of this systematic review and meta-analysis showed that the pooled prevalence of migraine in patients with IBD was 19% (95% CI: 15–22%).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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