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REVIEW

Spondyloarthritis in inflammatory bowel disease cohorts: systematic literature review and critical appraisal of study designs

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ABSTRACT

To critically appraise study designs evaluating spondyloarthritis (SpA) phenotypes in patients with inflammatory bowel disease (IBD). A systematic literature review of PubMed, Ovid, Scopus, Cinahl, Medline, Web of Science, and Cochrane databases was performed. Articles published from January 2000 - March 2020 were included if they evaluated the prevalence/incidence of musculoskeletal disease in cohorts of IBD patients. Most of the 69 included studies were clinic based (54/69, 78%), single center (47/69, 68%) and cross-sectional (60/69, 87%). The median prevalence of axial and peripheral SpA in IBD was 5% (range 1 - 46%) and 16% (range 1 - 43%), respectively. In 38 studies that evaluated axial disease in prospectively enrolled patients, inflammatory back pain was analyzed in 53%. SpA classification criteria were used in 68% and imaging was performed in 76%. In 35 studies that evaluated peripheral disease in prospectively enrolled patients, SpA classification criteria were used in 46%. A physical exam was performed in 74%, and it was performed by a rheumatologist in 54% of studies with a physical exam. Sub-phenotypes of peripheral SpA (mono- or oligo-arthritis, polyarthritis, enthesitis, dactylitis) were variably reported. Seventy-four percent of studies did not mention whether osteoarthritis and fibromyalgia had been assessed or excluded. The spectrum of SpA phenotypes in IBD patients remains incompletely characterized. Future studies should focus on standardizing the variables collected in IBD-SpA cohorts and defining musculoskeletal phenotypes in IBD-SpA in order to better characterize this disease entity and advance the field for clinical and research purposes.

Key messages

- Despite the prevalence of spondyloarthritis (SpA) in inflammatory bowel disease (IBD), it remains under recognised and understudied in both gastroenterology and rheumatology.
- Multiple IBD-SpA cohorts exist, however, overall IBD-SpA cohorts remain very heterogeneous with varying trial designs, evaluation protocols and outcome measures.
- Attempts at the identification and characterisation of SpA features are challenging as the SpA features themselves are highly variable from patient to patient and there is heterogeneity in the methodologies used to define these features.
- Future studies should focus on standardising the variables collected in IBD-SpA cohorts and defining SpA phenotypes in IBD-SpA in order to better characterise this disease entity and advance the field.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory illness of the gastrointestinal tract associated with various extraintestinal manifestations (EIMs) of which rheumatologic manifestations, which include peripheral and axial spondyloarthritis (SpA), are the most common. The prevalence of SpA in patients with IBD varies but is estimated to be as high as 46%.[1] Clinical evaluation of patients as well as research studies in IBD cohorts tend to be complex because they require, ideally, coordination between two different subspecialties. Most gastroenterologists are not sufficiently experienced to identify and differentiate inflammatory from degenerative musculoskeletal (MSK) disease or fibromyalgia. Conversely, rheumatologists are generally not secure in their ability to diagnose and distinguish IBD from other gastrointestinal manifestations such as irritable bowel syndrome or coeliac disease. Furthermore, the assessment and management of patients with SpA in IBD is hampered by an incomplete understanding of the pathogenesis, presentation and natural history of the SpA associated with IBD.

Data from several IBD-SpA cohorts have been published. Although a meta-analysis

assessing the incidence and prevalence of SpA in IBD has been previously reported,[2] we feel that a critical review of cohort design with particular attention to the process of collection of data regarding specific SpA phenotypes further adds to the literature as a significant gap in knowledge is how SpA subsets are defined in the setting of IBD.

In this paper, we review published data on existing IBD-SpA cohorts with a specific emphasis on study design from the rheumatologic perspective. This manuscript addresses the problems of consistency and fidelity in the description of SpA phenotypes in IBD studies. We hope that employing the findings of this review will permit future IBD-SpA cohorts to be more uniformly developed and will provide more consistent data for research and clinical care purposes.

METHODS

Literature search

A systematic literature review was performed using established best practices.[3] Databases PubMed, Ovid, Scopus, Cinahl, Medline, Web of Science and Cochrane were searched using four complementary search strategies (online supplemental table 1). The following terms were used: IBD, CD, UC, SpA, spondylitis, spondyloarthropathy, arthritis, ankylosing spondylitis (AS), enteropathic arthritis, sacroiliitis, MSK, articular, back pain, EIM. The literature search was performed in March of 2020 and dates for study inclusion were January 2000 to March 2020. Articles selected for inclusion were limited to full text, English language articles. Reviews, meta-analyses, case reports and paediatric studies were excluded. The reference lists of included studies were examined for additional studies eligible for inclusion.

Article titles were first reviewed for inclusion by one study investigator (MS). Abstracts and the full text were further screened by MS for final inclusion and confirmed by the co-authors (MHW, JE, KAK, SS). Studies were included if they evaluated the prevalence/incidence of SpA in a cohort of patients with IBD.

Data extraction

Data were extracted by one investigator (MS) and reviewed by the co-authors. A prespecified data extraction form was jointly developed (online supplemental table 2). The following data were collected: study setting and design, duration of follow-up, number of patients with IBD, type of IBD, use of SpA classification criteria, SpA phenotypes, method of rheumatologic evaluation, imaging modalities used (including imaging of symptomatic and/or asymptomatic participants) and rheumatologist involvement. Rheumatologist involvement was defined as mention of rheumatologist participation in the study or inclusion of at least one study author with a rheumatology affiliation. The prevalence and/or incidence of axial and peripheral SpA in the composite IBD group, individualised for CD and UC where available, was also collected.

We recorded how studies reported SpA. AS was defined by investigator opinion or by the modified New York criteria (mNY). Axial SpA (axSpA) was defined by investigator opinion, imaging evidence for axial inflammation or published classification criteria: Assessment of Spondyloarthritis International Society (ASAS),[4 5] European Spondyloarthropathy Study Group (ESSG),[6] Amor[7] or other.[8 9] Peripheral SpA (pSpA) was defined by investigator opinion or accepted classification criteria for pSpA (as above). If studies did not distinguish

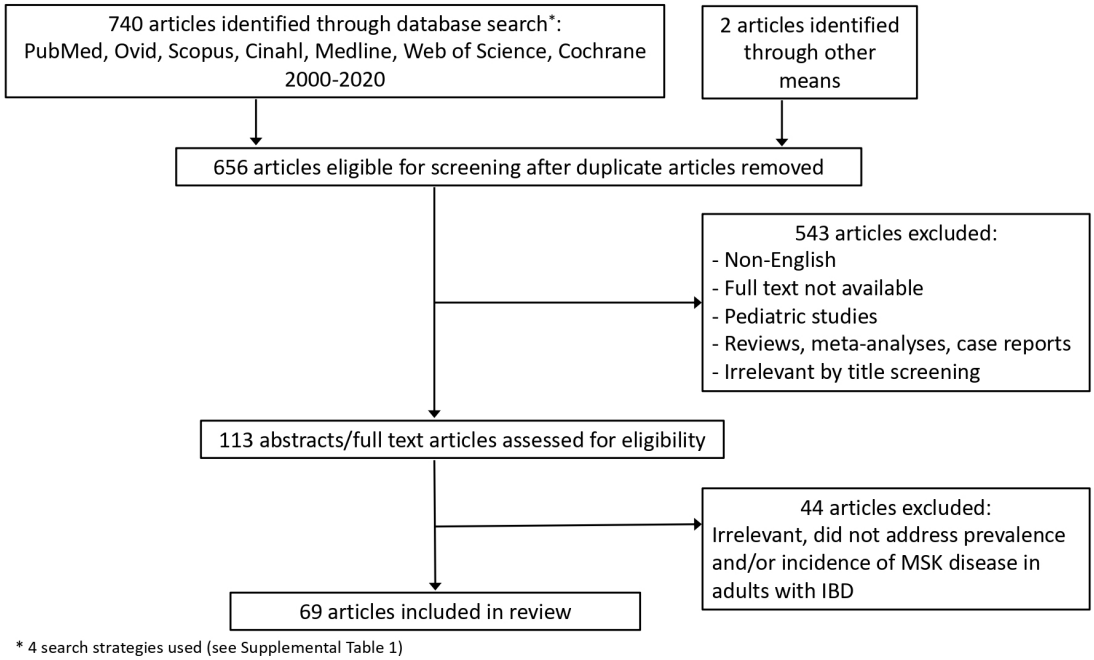

Figure 1 Article Selection. IBD, inflammatory bowel disease; MSK, musculoskeletal.

between axSpA and pSpA, we considered them as reporting SpA not otherwise specified (SpA NOS). Studies were further categorised and analysed based on whether the patients with IBD were prospectively enrolled or retrospectively analysed. Studies were categorised based on whether the patients with IBD were prospectively enrolled into a cohort from gastroenterology (GI) departments at the time the study was initiated and subsequently assessed either cross-sectionally or longitudinally. This is in contrast to retrospective chart review or claims database studies that did not enrol new patients into their study. We assumed that prospectively enrolled cohorts provide the optimal way to create future IBD-SpA cohorts because they define important variables in advance and collect the data in a consistent manner. Hence, we focused our analysis on prospectively enrolled cohorts only.

Patient and public involvement

There was no patient or public involvement in this research study.

Statistical analysis

Descriptive statistics (means or medians when the data were not normally distributed) were calculated using Microsoft Excel.

RESULTS

Literature review

We performed a systemic literature review of studies that evaluated axial and peripheral SpA phenotypes in IBD cohorts focusing on aspects of study design (figure 1). The initial database search yielded 740 articles; two additional articles were identified through bibliography review. Eighty-six articles were duplicates and removed, leaving 656 articles for screening. After removing non-English language articles, reviews, meta-analyses, paediatric studies and case reports, 113 studies remained for abstract/full text assessment. Of these, 44 studies were excluded because they did not address prevalence and/or incidence of SpA in IBD, resulting in 69 articles for critical review.

Study design characteristics

Major characteristics of the 69 individual studies are shown in online supplemental tables 3, 4). Focusing on study design, 54/69 (78%) were clinic-based and 15/69 (22%) were population-based. Forty-seven (68%) were single-centre and 22/69 (32%) were multicentre. Sixty studies (87%) were cross-sectional and 9/69 (13%) were longitudinal. The median duration of follow-up in the longitudinal studies was 3.5 years (range 1–25 years). The median age of patients at the time of the study was 41.9 years (range 32.6–50.6 years) and male patients made up a median of 49.6% studied patients (range 31.2%–100%). Most studies (36/69, 52%) originated in Europe, followed by the Near East (12/69, 17%), North America (10/60, 14%), Asia (8/69, 12%), South America (2/69, 3%) and Australia (1/69, 1%). The median number of patients with IBD across all studies was 247 patients (range 44–56 097 patients). Forty-four studies (64%) reported data separately for CD and UC, whereas 19 (27%) analysed either CD or UC. Six studies (9%) reported data for IBD without distinguishing between CD and UC. Undifferentiated IBD was reported in 9/69 (13%). Eight studies (11%) assessed for family history of SpA, 42/60 (61%) evaluated EIMs, however, only 7 (10%) evaluated for other comorbidities such as diabetes and hypertension, among others. Forty-five studies (65%) used some form of MSK imaging. Inflammatory back pain (IBP) was reported in 25/69 (36%). The prevalence and/or incidence of AS, axSpA, pSpA and SpA NOS was reported in 43/69 (62%), 47/69 (68%), 41/69 (69%) and 25/69 (36%), respectively. The median prevalence of AS/axSpA in IBD was 5% (range 1%–46%) and in pSpA 16% (range 1%–43%). Forty-five studies (65%) evaluated SpA phenotypes in prospectively enrolled patients with IBD (table 1): 28/45 (62%) evaluated both axSpA (including AS) and pSpA, 10/45 (22%) evaluated axSpA (including AS) only and 7/45 (16%) evaluated pSpA only. The following sections will examine these studies in greater detail.

Axial disease in IBD: study characteristics

In studies that evaluated axial disease (table 2), the presence of IBP was analysed in 20/38 (53%). Twenty-six (68%) used established SpA classification criteria. Modified New York, ASAS, ESSG and Amor criteria were used in 17/38 (45%), 11/38 (29%), 8/38 (21%) and 3/38 (8%), respectively. Some studies used more than one set of classification criteria. The ASAS classification criteria have been increasingly used since their publication in 2009.[4 5] A similar fraction of papers published in 2009 or later did not use any SpA criteria compared with studies published before 2009 (33% vs 29%). However, 69% of the studies published after 2014 incorporated ASAS classification criteria, compared with 0% of the studies published from 2009 to 2014.

Rheumatologists were involved in 30/38 (79%) studies. A physical examination was included in 29/38 (76%), which was performed by a rheumatologist in 18/38 (47%). Other methods of clinical evaluation included self-report in 6/38 (16%) and medical record review in 6/38 (16%).

Axial disease in IBD: imaging

Imaging was performed in 29/38 (76%) of all studies evaluating axial disease (table 2). The frequency of imaging modalities used was as follows: X-ray of the pelvis or sacroiliac joints (SIJ) in 18/38 (47%), X-ray of the spine in 11/38 (29%), MRI of the pelvis/SIJ 7/38 (18%), MRI of the spine in 2/39 (5%) and CT of the pelvis/SIJ in 4/38 (11%). Imaging of the intestine such as CT or MR enterography (MRE) were re-analysed for SpA phenotypes in 1/38 (3%). Seven studies (18%) did not specify what axial locations had been imaged. MRI of

Table 1 Study characteristics—prospectively enrolled cohorts

Study	Setting	Site	Design	Patients with IBD (n)	IBD type	SpA criteria	SpA evaluation	Rheum input
Al-Jarallah *et al* 2012[33]	Clinic	SC	CS	125	CD/UC	–	Exam—other	No
Al-Jarallah *et al* 2013[34]	Clinic	SC	CS	130	CD/UC	–	Exam—other	No
Bandinelli *et al* 2011[24]	Clinic	SC	CS	121	CD/UC	–	Exam—rheum	Yes
Bandinelli *et al* 2014[35]	Clinic	SC	Long	81	CD/UC	mNY	Exam—rheum	Yes
Bandyopadhyay *et al* 2015[36]	Clinic	SC	CS	120	CD/UC	ASAS (A)	Exam—rheum	Yes
Barreiro-de Acosta *et al* 2007[37]	Clinic	SC	CS	173	CD	–	Exam—rheum	Yes
Bertolini *et al* 2020[38]	Clinic	MC	CS	148	CD/UC	ASAS (A/P)	Exam—rheum	Yes
Beslek *et al* 2009[39]	Clinic	SC	CS	122	CD/UC	mNY, ESSG	Exam—rheum	Yes
Christodoulou *et al* 2002[40]	Clinic	SC	CS	256	CD/UC	–	Self-report, chart	No
D'Inca *et al* 2009[41]	Clinic	MC	Long	651	CD/UC	ESSG, mNY	Exam—rheum	Yes
De Vlam *et al* 2000[42]	Clinic	SC	CS	103	CD/UC	ESSG, mNY	Exam—rheum	Yes
Ditisheim 2015[43]	Pop	MC	CS	2401	CD/UC	ASAS (P)	Self-report	Yes
Dmowska-Chalaba *et al* 2015[44]	Clinic	SC	CS	51	CD/UC	ASAS (A/P)	Exam—other	Yes
Duricova *et al* 2017[45]	Pop	MC	CS	628	UC	–	Exam—other	No
Fatemi *et al* 2016[46]	Clinic	SC	CS	273	CD/UC	mNY	Exam—rheum	Yes
Gotler *et al* 2015[47]	Clinic	SC	CS	286	CD/UC	ASAS (A)	Self-report, chart	Yes
Hammoudeh *et al* 2018[48]	Clinic	SC	CS	127	CD/UC	ASAS (A/P)	Exam—rheum	Yes
Hiller *et al* 2019[49]	Pop	MC	Long	3298	CD/UC	–	Exam—other	Yes
Isene *et al* 2015[50]	Pop	MC	Long	1145	CD/UC	–	Exam—other	Yes
Kamo 2015[51]	Clinic	SC	CS	137	CD/UC	–	Self-report	No
Karmiris *et al* 2016[52]	Clinic	MC	CS	1860	CD/UC	–	Exam—rheum	Yes
Lakatos *et al* 2003[53]	Clinic	SC	Long	873	CD/UC	–	Exam—rheum	Yes
Lanna *et al* 2008[54]	Clinic	SC	CS	130	CD/UC	mNY	Exam—rheum	Yes
Luchetti *et al* 2019[55]	Clinic	SC	Long	262	CD/UC	ASAS (A/P)	Exam—rheum	Yes
Mocelin *et al* 2015[56]	Clinic	SC	CS	100	CD	ASAS (A/P)	Chart	Yes
Orchard *et al* 2009[57]	Clinic	SC	CS	44	CD	mNY*	Exam—other	No
Ossum *et al* 2018 (A)[13]	Pop	MC	CS	470	CD/UC	ASAS (A), mNY	Self-report†	Yes
Ossum *et al* 2018 (P)[14]	Pop	MC	CS	470	CD/UC	ASAS (P)	Self-report†	Yes
Palm *et al* 2001[15]	Pop	MC	CS	521	CD/UC	mNY	Exam—rheum	Yes
Palm *et al* 2002[16]	Pop	MC	CS	406	CD/UC	mNY, ESSG	Exam—rheum	Yes
Peeters, 2008[58]	Clinic	MC	CS	251	CD	mNY	Chart	Yes
Picchianti-Diamanti *et al* 2020[59]	Clinic	MC	CS	347	CD/UC	ASAS (A/P)	Exam—rheum	Yes
Pokharna *et al* 2004[60]	Clinic	SC	CS	46	UC	mNY	Exam—other	No
Queiro *et al* 2000[61]	Clinic	SC	Long	62	CD/UC	Amor, ESSG, mNY	Exam—other	Yes
Ricart *et al* 2004[62]	Clinic	SC	CS	243	CD/UC	–	Self-report	No
Rovisco *et al* 2016[63]	Clinic	SC	CS	76	CD/UC	ASAS (A/P)	Exam—rheum	Yes

Continued

Table 1 Continued

Study	Setting	Site	Design	Patients with IBD (n)	IBD type	SpA criteria	SpA evaluation	Rheum input
Sahli *et al* 2018[64]	Clinic	SC	CS	64	CD/UC	ASAS (A), Amor	Exam—rheum	Yes
Salvarani *et al* 2001[65]	Clinic	MC	CS	160	CD/UC	mNY, ESSG	Exam—rheum	Yes
Steer *et al* 2003[66]	Clinic	SC	CS	134	CD	mNY	Exam—other	Yes
Stolwijk *et al* 2013[67]	Clinic	SC	CS	350	CD/UC	–	Self-report, chart	Yes
Subramaniam *et al* 2015[68]	Clinic	SC	CS	140	CD/UC	ASAS (A/P)	Self-report, chart	Yes
Turkcapar *et al* 2006[69]	Clinic	SC	CS	162	CD/UC	mNY, ESSG	Exam—rheum	Yes
Van Erp *et al* 2016[70]	Clinic	SC	Long	255	CD/UC	ASAS (A/P), Amor, ESSG, mNY	Exam—other	Yes
Vavricka *et al* 2011	Pop	MC	CS	950	CD/UC	–	Physician survey	No
Yuksel *et al* 2011[71]	Clinic	SC	CS	357	CD/UC	–	Exam—rheum	Yes

*Adapted for MRI.
†Used rheumatologist physical examination from 5-year follow-up study.
A, axial; ASAS, Assessment of Spondyloarthritis International Society; CD, Crohn's disease; CS, cross-sectional; ESSG, European Spondyloarthropathy Study Group; IBD, inflammatory bowel disease; Long, longitudinal; MC, multicentre; mNY, modified New York criteria; P, peripheral; Pop, population; Rheum, rheumatologist; SC, single centre; SpA, spondyloarthritis; UC, ulcerative colitis.

the pelvis/SIJ was only performed in studies published in 2009 or later. Fourteen studies (48%) imaged both symptomatic and asymptomatic patients while 7/29 (24%) imaged symptomatic patients only. Eight studies (28%) did not specify whether imaging was done in symptomatic or asymptomatic patients.

Peripheral joint disease in IBD: study characteristics

Thirty-five of 69 studies (51%) evaluated peripheral joint disease (table 3). SpA criteria (ASAS, ESSG, Amor) were employed to define peripheral disease in 16/35 (46%). Three studies specifically excluded patients with osteoarthritis (OA) or fibromyalgia and six studies recorded the presence OA and/or fibromyalgia. The majority of studies, 26/35 (74%), did not mention whether OA and fibromyalgia were assessed.

Direct rheumatologist involvement was recorded in 28/35 (80%) studies. A physical examination performed by any provider was done in 26/35 (74%) and physical examination by a rheumatologist was performed in 19/35 (54%). Self-report was used in 7/35 (20%) and medical record review was used in 12/35 (34%).

Peripheral joint disease in IBD: imaging

Peripheral joint imaging was performed in 14/35 (40%) studies evaluating peripheral disease in IBD cohorts. X-ray of peripheral joints was done in 8/35 (23%), ultrasound in 5/35 (14%) and whole-body scintigraphy in 1/35 (3%). Four of the studies that incorporated ultrasound used formal/validated ultrasound outcome measures.[10 11] Three of the five ultrasound studies explicitly imaged asymptomatic patients. Peripheral imaging was used in less than half of the studies, and despite the general widespread and increasing use in rheumatology, ultrasound was infrequently used.

Peripheral joint disease in IBD: sub-phenotype evaluation

Twenty-seven (77%) of the studies that evaluated peripheral disease in IBD cohorts characterised peripheral SpA in more detail. Enthesitis was analysed in 18/27 (67%), monoarthritis or oligoarthritis in 13/27 (48%), dactylitis in 13/27 (48%), arthralgia in 12/27 (44%) and polyarthritis in 10/26 (39%). Two studies analysed all of these five sub-phenotypes, three studies analysed four phenotypes, seven studies analysed three phenotypes, nine studies analysed two phenotypes, four studies analysed one phenotype and two studies only reported other phenotypes such as fibromyalgia, OA or bursitis. Data for type 1 and type 2 arthritis were reported in six studies; type 1 and type 2 arthritis is a categorisation of IBD-associated arthritis described and used exclusively in the GI literature.[12] Type 1 arthritis describes an acute and self-limiting oligoarthritis that parallels IBD activity while type 2 arthritis describes a chronic, symmetric polyarthritis that does not parallel IBD activity.

A physical examination by a rheumatologist was performed in 19/35 (54%) of the studies that assessed peripheral joint disease. Of these studies, 95% distinguished patients by different characteristics of peripheral SpA manifestations (monoarthritis or oligoarthritis, polyarthritis, enthesitis, dactylitis, arthralgia). Fifty-three per cent (10/19) used pSpA classification criteria, and 10/19 (53%) had peripheral imaging performed. In

Table 2 Study characteristics—studies evaluating axial joint disease

Study	SpA criteria	Physical exam	Exam provider	Other evaluation	Axial phenotype	Axial imaging	Subjects imaged
Al-Jarallah *et al* 2012[33]	–	Yes	Other	–	AxSpA	MRI spine MRI pelvis/SIJ X-ray*	Sx/aSx
Al-Jarallah *et al* 2013[34]	–	Yes	Other	–	AS, axSpA	–	–
Bandinelli *et al* 2014[35]	mNY	Yes	Rheum	–	AxSpA	X-ray pelvis/SIJ MRI pelvis/SIJ	Sx/aSx
Bandyopadhyay et al 2015[36]	ASAS	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine MRI pelvis/SIJ MRI spine	Sx/aSx
Barreiro-de Acosta *et al* 2007[37]	–	Yes	Rheum	–	AS, axSpA	X-ray*	Sx
Bertolini *et al* 2020[38]	ASAS	Yes	Rheum	–	AxSpA	MRI pelvis/SIJ	Sx/aSx
Beslek *et al* 2009[39]	mNY, ESSG	Yes	Rheum	–	AS	X-ray pelvis/SIJ MRI pelvis/SIJ	Sx
Christodoulou *et al* 2002[40]	–	No	–	Self-report, chart	AxSpA	–	–
D'Inca *et al* 2009[41]	ESSG, mNY	Yes	Rheum	–	AS, axSpA	X-ray spine MRI spine X-ray hip MRI hip bone scintigraphy	Sx
De Vlam *et al* 2000[42]	ESSG, mNY	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ	Sx/aSx
Dmowska-Chalaba *et al* 2015[44]	ASAS	Yes	Other	–	AxSpA	X-ray and MRI*	–
Duricova *et al* 2017[45]	–	Yes	Other	–	AxSpA	–	–
Fatemi *et al* 2016[46]	mNY	Yes	Rheum	–	AS	X-ray pelvis/SIJ	Sx
Gotler *et al* 2015[47]	ASAS	No	–	Self-report, chart	AxSpA	CT pelvis/SIJ GI studies analysed for axial phenotypes	Sx/aSx
Hammoudeh *et al* 2018[48]	ASAS	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine	–
Hiller *et al* 2019[49]	–	Yes	Other	–	AS	–	–
Isene *et al* 2015[50]	–	Yes	Other	–	AS, axSpA	–	–
Karmiris *et al* 2016[52]	–	Yes	Rheum	–	AS, axSpA	X-ray and MRI*	–
Lakatos *et al* 2003[53]	–	Yes	Rheum	–	AxSpA	X-ray and MRI*	–
Lanna *et al* 2008[54]	mNY	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine	Sx/aSx
Luchetti *et al* 2019[55]	ASAS	Yes	Rheum	–	AS, axSpA	X-ray and MRI*	Sx
Mocelin *et al* 2015[56]	ASAS	No	–	Chart	AS, axSpA	–	–
Orchard *et al* 2009[57]	mNY†	Yes	Other	–	AS, axSpA	MRI pelvis/SIJ	Sx/aSx
Ossum *et al* 2018 Axial[13]	ASAS, mNY	No	–	Self-report	AS, axSpA	X-ray pelvis/SIJ X-ray spine	–
Palm *et al* 2001[15]	mNY	Yes	Rheum	–	AS	–	–
Palm *et al* 2002[16]	mNY, ESSG	Yes	Rheum	–	AS	X-ray pelvis/SIJ X-ray spine	–
Peeters *et al* 2008[58]	mNY	No	–	Chart	AS, axSpA	X-ray pelvis/SIJ	Sx/aSx

Continued

Table 2 Continued

Study	SpA criteria	Physical exam	Exam provider	Other evaluation	Axial phenotype	Axial imaging	Subjects imaged
Pokharna *et al* 2004[60]	mNY	Yes	Other	–	AxSpA	X-ray pelvis/SIJ X-ray spine	Sx/aSx
Queiro *et al* 2000[61]	Amor, ESSG, mNY	Yes	Other	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine	Sx/aSx
Ricart *et al* 2004[62]	–	No	–	Self-report	AS	–	–
Sahli *et al* 2018[64]	ASAS, Amor	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine MRI pelvis/SIJ CT pelvis/SIJ	Sx/aSx
Salvarani *et al* 2001[65]	mNY, ESSG	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ	–
Steer *et al* 2003[66]	mNY	Yes	Other	–	A AS, axSpA	X-ray pelvis/SIJ CT pelvis/SIJ	Sx
Stolwijk *et al* 2013[67]	–	No	–	Self-report, chart	AxSpA	–	–
Subramaniam *et al* 2015[68]	ASAS	No	–	Self-report, chart	AS, axSpA	X-ray pelvis/SIJ	Sx/aSx
Turkcapar *et al* 2006[69]	mNY, ESSG	Yes	Rheum	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine CT pelvis/SIJ	Sx/aSx
Van Erp *et al* 2016[70]	ASAS, Amor, ESSG, mNY	Yes	Other	–	AS, axSpA	X-ray pelvis/SIJ X-ray spine	Sx
Vavricka *et al* 2011	–	No	–	Physician survey	AS	X-ray*	–

*Axial location not specified.
†Adapted for MRI.
AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; aSx, asymptomatic; AxSpA, axial spondyloarthritis; CT, CAT Scan; ESSG, European Spondyloarthropathy Study Group; GI, gastrointestinal; mNY, modified New York critiera; Rheum, rheumatologist; SIJ, sacroiliac joint; SpA, spondyloarthritis; Sx, symptomatic.

7/35 (20%), a physical examination was performed by a non-rheumatologist provider. Of these studies, only 4/7 (57%) distinguished patients by arthritis sub-phenotype. Twenty-nine per cent (2/7) used pSpA classification criteria, and 3/7 (43%) used peripheral imaging. In the remaining nine studies (26%), no physical examination was performed. Of these studies without a physical examination, 5/9 (56%) distinguished patients by arthritis sub-phenotype, 4/9 (44%) used pSpA classification criteria, 1/9 (11%) used peripheral imaging.

DISCUSSION

In this systematic review of 69 studies that analysed SpA manifestations in IBD cohorts, we found that most were clinic-based (78%), single-centre (68%) and cross-sectional (87%) in design. The median number of patients with IBD was 247 (range 44–56 097 patients) and the median prevalence of axSpA and pSpA in IBD was 5% (range 1%–46%) and 16% (range 1%–43%), respectively. Thirty-eight studies evaluated axial disease in prospectively enrolled patients with IBD. Of these 38 studies, the presence of IBP was analysed in 53%, SpA classification criteria were used in 68% and imaging was performed in 76%. Peripheral SpA was evaluated in prospectively enrolled patients in 35 studies. Of these 35 studies, SpA classification criteria were used in 46% and imaging was done 40%. A physical examination was performed in 74%, and in 54% of these studies, it was done by a rheumatologist. Sub-phenotypes of pSpA (monoarthritis or oligoarthritis, polyarthritis, enthesitis, dactylitis) or arthralgia were variably reported, and 74% of the studies did not mention whether OA and fibromyalgia had been assessed or excluded.

IBD-SpA is a heterogenous, multifaceted disease. Of the 69 studies included in this review, most were single centre, and the median number of patients enrolled was only 247. This number is unlikely to be sufficient to describe the full spectrum of IBD-SpA, and larger, multicentre cohorts are needed to better define IBD-SpA. The majority of studies were clinic-based, most commonly

Table 3 Study characteristics—studies evaluating peripheral joint disease

Study	Sub-phenotype	Major phenotypes*	Other descriptions	Physical exam—provider	Other evaluation	Imaging†	Subjects imaged
Al-Jarallah *et al* 2012[33]	Yes	Dactylitis, enthesitis	Type 1/type 2	Yes—other	–	–	–
Al-Jarallah *et al* 2013[34]	Yes	Dactylitis, enthesitis	Type 1/type 2	Yes—other	–	–	–
Bandinelli *et al* 2011[24]	Yes	Enthesitis	–	Yes—Rheum	–	US	aSx
Bandyopadhyay *et al* 2015[36]	Yes	Other	Type 1/type 2	Yes—Rheum	–	–	–
Barreiro-de Acosta *et al* 2007[37]	No	–	–	Yes—Rheum	–	–	–
Bertolini *et al* 2020[38]	Yes	Monoarthritis/ oligoarthritis/ polyarthritis, dactylitis, enthesitis, arthralgia	–	Yes—Rheum	–	US	Sx/aSx
Beslek *et al* 2009[39]	Yes	Monoarthritis/ oligoarthritis, enthesitis	Chronic arthritis	Yes—Rheum	–	–	–
Christodoulou *et al* 2002[40]	Yes	Monoarthritis/ oligoarthritis, arthralgia	–	No	Self-report, chart	–	–
D'Inca *et al* 2009[41]	Yes	Monoarthritis/ oligoarthritis, polyarthritis, arthralgia	Symmetrical arthritis,‡ fibromyalgia, tendinitis	Yes—Rheum	–	Bone scintigraphy	Sx
DeVlam *et al* 2000[42]	Yes	Monoarthritis/ oligoarthritis, dactylitis, enthesitis, arthralgia	Polyarticular asymmetric	Yes—Rheum	–	–	–
Ditisheim *et al* 2015[43]	No	–	–	No	Self-report	–	–
Duricova *et al* 2017[45]	No	–	–	Yes—Other	Chart	–	–
Fatemi *et al* 2016[46]	Yes	Monoarthritis/ oligoarthritis/ polyarthritis, arthralgia	Fibromyalgia	Yes—Rheum	—	—	—
Hammoudeh *et al* 2018[48]	Yes	Enthesitis, arthralgia	Type 1/type 2	Yes—Rheum	–	–	–
Isene *et al* 2015[50]	No	–	–	Yes—Other	–	–	–
Kamo *et al* 2015[51]	Yes	Dactylitis, enthesitis, arthralgia	–	No	Self-report	–	–

Continued

Table 3 Continued

Study	Sub-phenotype	Major phenotypes*	Other descriptions	Physical exam—provider	Other evaluation	Imaging†	Subjects imaged
Karmiris *et al* 2016[52]	Yes	Arthralgia	Monoarthralgia/oligoarthralgia, polyarthralgia	Yes—Rheum	–	–	–
Lakatos *et al* 2003[53]	Yes	Other	Type 1/type 2	Yes—Rheum	–	–	–
Lanna *et al* 2008[54]	Yes	Monoarthritis/oligoarthritis/polyarthritis, enthesitis	Asymmetric arthritis,§ inflammatory arthalgia¶	Yes—Rheum	–	X-ray	Sx/aSx
Luchetti *et al* 2019[55]	Yes	Monoarthritis/oligoarthritis/polyarthritis, enthesitis	OA, fibromyalgia	Yes—Rheum	–	US	Sx
Mocelin *et al* 2015[56]	No	No**	Fibromyalgia	No	Chart	–	–
Ossum *et al* 2018: Peripheral[14]	Yes	Dactylitis, enthesitis	pArthritis, pSpA	No	Self-report	X-ray	Sx
Palm *et al* 2001[15]	Yes	Polyarthritis, dactylitis, enthesitis	Symmetrical arthritis,‡ OA	Yes—Rheum	–	X-ray	Sx
Peeters *et al* 2008[58]	No	–	–	No	Chart	–	–
Picchianti-Diamanti *et al* 2020[59]	Yes	Monoarthritis/oligoarthritis/polyarthritis, dactylitis††	Type 1/type 2	Yes—Rheum	–	US	–
Pokharna *et al* 2004[60]	Yes	Monoarthritis/oligoarthritis, arthralgia	–	Yes—Other	–	X-ray	Sx/aSx
Queiro *et al* 2000[61]	No	–	Asymmetric arthritis§	Yes—Other	–	X-ray	Sx/aSx
Rovisco *et al* 2016[63]	Yes	Enthesitis	–	Yes—Rheum	–	US	Sx/aSx
Salvarani *et al* 2001[65]	Yes	Monoarthritis/oligoarthritis/polyarthritis, dactylitis, enthesitis	–	Yes—Rheum	–	–	–
Stolwijk *et al* 2013[67]	Yes	Dactylitis, enthesitis	Fibromyalgia	No	Self-report, chart	–	–
Subramaniam *et al* 2015[68]	Yes	Dactylitis, enthesitis	–	No	Self-report, chart	–	–

Continued

Table 3 Continued

Study	Sub-phenotype	Major phenotypes*	Other descriptions	Physical exam—provider	Other evaluation	Imaging†	Subjects imaged
Turkcapar *et al* 2006[69]	Yes	Monoarthritis/ oligoarthritis/ polyarthritis, dactylitis, enthesitis	–	Yes—Rheum	–	X-ray	Sx/aSx
Van Erp *et al* 2016[70]	Yes	Monoarthritis/ oligoarthritis/ polyarthritis, dactylitis, enthesitis, arthralgia	–	Yes—Other	–	X-ray	Sx
Vavricka *et al* 2011	No	–	–	No	Physician survey	–	–
Yuksel *et al* 2011[71]	Yes	Arthralgia	Symmetrical arthritis,‡ fibromyalgia, tendinitis	Yes-Rheum	–	X-ray	Sx

*Peripheral phenotypes: monoarthritis/oligoarthritis, polyarthritis, dactylitis, enthesitis, arthralgia.
†Peripheral Imaging only.
‡Did not specify polyarthritis.
§Number of joints not specified.
¶Noted no swelling but did not define further.
**Joint symptoms reported exclusively as arthralgia—no mention of arthritis.
††Ultrasound recorded synovial hypertrophy, enthesitis and tenosynovitis, but did not report enthesitis separately.
OA, osteoarthritis; pArthritis, peripheral arthritis; pSpA, peripheral spondyloarthritis; Rheum, rheumatologist; US, Ultrasound; Sx, symptomatic; aSx, asymptomatic

at tertiary care centres, which may not capture a group of patients representative of the entire population of IBD-SpA. The majority of studies were cross-sectional, a design that does not permit an evaluation of the natural history of disease or the detection of incident SpA in IBD. In the Inflammatory Bowel South-Eastern Norway studies, which evaluated SpA in patients with IBD over a 20-year period,[13–16] the prevalence of pSpA increased from 11.9% at 5 years to 26.1% at 20 years, and the prevalence of AS increased from 3.7% at 5 years to 4.5% at 20 years, illustrating that longitudinal studies capture additional patients that are missed in cross-sectional studies.

Across all 69 studies, we found that the composite median prevalence of axSpA and pSpA in IBD was 5% (range 1%–46%) and 16% (range 1%–43%), respectively; similar to what has been reported previously in a meta-analysis.[2] However, the range of IBD-SpA prevalence values across the studies was wide. This may be a result of the variable definition of IBD-SpA across the studies, which ranged from clinical, physician diagnosis to multiple different SpA classification criteria. The characterisation of axial disease in IBD-SpA cohorts varied despite established classification and imaging criteria.[4] Inflammatory back pain, an important screening tool for axSpA, was only evaluated in 53% of the 38 studies that assessed axial disease prospectively. Most of the 35 studies that assessed peripheral disease prospectively did not address whether other MSK conditions, such as OA and fibromyalgia, were excluded, which likely confounds the reports of SpA prevalence. Many studies were retrospective and/or claims database studies which may bias findings based on how patients are identified and how patient data are recorded. The range of prevalence of SpA in IBD is wide, and more uniform definitions of SpA in IBD are necessary to better understand the true frequency of SpA in IBD.

Despite accepted imaging criteria used in the evaluation of axSpA[4] and the prominent role of MRI in the diagnosis and classification of axSpA,[4] imaging was not always employed in the 38 studies that assessed axial disease prospectively. MRE, a technique that images the bowel, is an important tool used in the evaluation of IBD, and often serendipitously captures information about the SI joints. Though MRE is suboptimal for assessment of the SIJ, the utility of using MRE as a screening tool has been demonstrated,[17] however, the routine utility of this modality remains unclear. Furthermore, it is unknown whether axSpA in IBD is different from axSpA in patients without IBD. Studies in psoriatic arthritis (PsA) have indicated that axial PsA is distinct from AS/axSpA.[18 19] Early radiographic studies[20] suggest that axial disease in AS and IBD are morphologically similar, though further research is needed to better define this clinical phenotype.

Ultrasound is increasingly being used in the identification of inflammatory arthritis.[21] However, very few studies (14%) used ultrasound to assess peripheral SpA in the 35 studies that addressed peripheral SpA in prospectively enrolled patients with IBD. Ultrasound can objectively identify tenosynovitis or enthesitis, which can aid in early diagnosis and has been shown to predict the transition from psoriasis to PsA.[22 23] Similarly, studies included in this review demonstrated evidence of enthesial disease and erosions in asymptomatic patients with IBD,[24] identifying subclinical SpA. Ultrasound has the potential provide a unique opportunity to assess SpA, in particular early disease, in IBD.

While it is well-documented that SpA is the most common EIM in IBD, relatively little is known about clinical sub-phenotypes. Only a small fraction of the 35 studies that assessed peripheral disease prospectively analysed the whole SpA spectrum of IBD-SpA that includes axial disease, monoarthritis or oligoarthritis, polyarthritis, dactylitis and enthesitis. This assessment may have important therapeutic implications. For example, in patients with predominant enthesitis, a biologic may provide efficacy that supersedes conventional synthetic disease modifying anti-rheumatic medications.[25–27] The categorisation of SpA in IBD as type 1 and 2 arthritis[12] has not been validated prospectively, though the use of this categorisation persists in the gastrointestinal literature and in clinical care. A granular categorisation of the SpA phenotype, perhaps including type 1 and 2 designations, may provide important insights into pathogenesis. Additionally, some of these studies identified arthralgia, though often did not specify other conditions such as fibromyalgia and OA which are common conditions in the general population. Fibromyalgia has been demonstrated in up to 30% of patients with IBD,[28] however, only about 1/3 of the 35 studies that assessed peripheral disease prospectively made any note of OA or fibromyalgia. From a management perspective, it is critical to identify these entities as therapy for these conditions is vastly different.

Among all prospectively enrolled cohorts evaluated, not all studies used SpA classification criteria, and when employed, there was a range of classification criteria used. We observed a strong recent trend to apply ASAS classification criteria. The ASAS criteria were developed for use in SpA. IBD-SpA may have different clinical characteristics much as axial PsA demonstrates different characteristics when compared with AS.[18 19] The performance of the ASAS criteria in IBD-SpA has not been studied in sufficient detail to know if they are applicable. For instance, an elevated serum CRP level is listed in the ASAS SpA criteria, however, this can be elevated independently in IBD and may not be reflective of SpA activity. ASAS criteria include HLA-B27 status. While the prevalence of HLA-B27 in AS in 85%–90%,[29] it is much lower in IBD-SpA, reported in up to 60%.[29]

Our study reported herein has several strengths and limitations. While prior studies have looked at the prevalence/incidence of SpA in IBD, to the best of our knowledge, this is the first study that systematically and comprehensively investigated study design and characteristics of SpA phenotyping in IBD. The systematic literature review was performed using established best

practices[3] and differences of study design were identified. Limitations of this study include restricting the review to English language articles. The study focused on adult disease, and future research should include characterising paediatric IBD-SpA. Our study was limited by incomplete or absent reporting of variables such as imaging of asymptomatic patients as well as the presence of OA and fibromyalgia. Additionally, full descriptions of the individual locations that were imaged were not always present. We did not record whether laboratory or pathology data had been collected. Finally, we did not compare how different study settings affect prevalence rates. Studies were identified and data extraction were performed by a single member of the group, rather than done in duplicate, though data were discussed by the entire group.

CONCLUSION

Although patients with IBD and SpA appear to share many clinical, immunologic and genetic characteristics,[30–32] the exact relationship between these two entities has never been comprehensively defined. Attempts at identification and characterisation of the SpA features in IBD are beset with two problems; SpA features themselves are highly variable from patient to patient and there is heterogeneity in the methodologies used to define these features. Of importance, it is not clear that standard accepted SpA classification criteria developed independently without consideration of IBD status are entirely applicable to IBD patients with SpA. Developing a standard set of variables to be collected in IBD-SpA cohorts will allow for a better definition of SpA phenotypes in IBD-SpA. A concrete characterisation of these features will facilitate future research endeavours and ultimately improve patient management.

Based on our data, we conclude that a study that attempts to comprehensively describe axial and peripheral SpA phenotypes in IBD requires a large number of patients from a range of settings. Therefore, an ideal study would be multicentre and population-based. However, initiating a clinic-based or region-based study may be a more practical starting point. Patients should be followed longitudinally. Ideally and before any further work is done, validation of prior SpA classification tools (such as the ASAS classification criteria) should take place in patients with IBD. The set of clinical variables collected should include IBP and the exclusion of other inflammatory and non-inflammatory MSK conditions such as OA and fibromyalgia. A physical examination should always be performed, ideally by a rheumatologist or, alternatively, by a trained healthcare provider, and data on arthritis patterns and presence of enthesitis or dactylitis should be collected. At a minimum, imaging with both plain radiographs and MRI of the SIJs should be performed, and the assessment of peripheral disease should incorporate ultrasound. Finally, research participants should be followed longitudinally with formal semiannual evaluations and intermittent assessments as needed for disease flares. The ideal starting point would be a joint effort by gastroenterologists and rheumatologists to create a joint statement that defines IBD-SpA.

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