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Musculoskeletal manifestations in children with inflammatory bowel disease: a multicenter cohort study (GASTROREUM study)

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Abstract

Background Musculoskeletal (MSK) symptoms are the most common extra-articular manifestations of pediatric-onset inflammatory bowel diseases (pIBD), and are associated with a more aggressive disease course. This study aims to characterize MSK manifestations in patients with pIBD, and to seek for predictors of persistently active arthritis one year after pIBD diagnosis.

Methods A multicenter, retrospective cohort study was conducted at 25 Italian pediatric rheumatology centers. Patients aged < 18 years with pIBD and MSK manifestations, followed for at least one year, were included. Data at onset of first MSK symptom, pIBD diagnosis, and one-year follow-up visit following pIBD diagnosis were collected.

Results A total of 180 patients were included, 111 (61.7%) with Crohn's disease (CD), 55 (30.5%) with ulcerative colitis (UC), and 14 (7.8%) with unclassified IBD (IBDU). Arthralgia (72.8%) and arthritis (69.4%), were the most frequent MSK manifestations. Patients with CD had MSK symptoms prior to pIBD diagnosis more frequently than those with UC/IBDU (51.4% vs. 40.6%). Among the 125 patients with arthritis, 76.8% had peripheral arthritis, 14.4% had axial disease, and 8.8% had both peripheral and axial involvement. The most common articular pattern was oligoarthritis (52.0%), followed by monoarthritis (26.4%) and polyarthritis (21.6%). The most frequently affected joints were the knee,

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ankle, and hip**.** On multivariable analysis, antinuclear antibody (ANA) positivity (OR = 3.05, 95% CI: 1.05 – 8.89) and a polyarticular course of arthritis (OR = 3.42, 95% CI: 1.13–10.38) were independently associated with persistence of active arthritis at year 1 after pIBD diagnosis.

Conclusions Most patients with pIBD and arthritis presented with peripheral oligoarthritis affecting lower limb joints. A positive ANA status and development of polyarthritis predicted sustained arthritis activity.

Keywords Inflammatory bowel disease, Children, Musculoskeletal, Arthritis, Sacroiliitis, Juvenile idiopathic arthritis, Antinuclear antibodies

Background

Inflammatory bowel disease (IBD) is an umbrella term that embraces a group of chronic disorders characterized by persistent or recurrent inflammation of the gastrointestinal tract. Its clinical spectrum includes Crohn's disease (CD), ulcerative colitis (UC), and unclassified IBD (IBDU) [1]. In up to 25% of cases, IBD manifests before the age of 18, and onset in childhood is often associated with a severe disease phenotype and course [2].

The inflammatory process in IBD is not restricted to the gut, but may virtually affect any organs and systems, including the musculoskeletal (MSK), ocular, dermatologic, and hepatic [3–7]. MSK symptoms, especially arthralgia and arthritis, are the most common extra-articular manifestations of IBD [8, 9]. Given the similarities in the pathogenic immune responses between the gut and the joints, as well as the observed temporal relationship between inflammation in these regions, it is hypothesized that inflammatory events developing in the gut may trigger an inflammatory process in the joints, thus suggesting a causative link [10]. MSK manifestations may have a relevant impact as their occurrence has been associated with a more aggressive disease course and an increased need for biologic therapy and surgery [11, 12].

The reported prevalence of MSK manifestations in adults with IBD varies but is estimated to be up to 46% [13]. Gastroenterologists recognize 3 patterns of arthritis in IBD: Type I, a peripheral arthritis affecting fewer than five joints, often mirroring intestinal inflammation; Type II, a non-symmetric polyarthritis involving five or more peripheral joints, usually independent of IBD activity; and Type III, an axial arthritis, sometimes with peripheral joint involvement, also unrelated to IBD activity. Type I arthritis can precede IBD diagnosis, while Types II and III typically do not [14]. In the rheumatology field, IBD-associated arthropathy is included, according to the Assessment of Spondyloarthritis International Society (ASAS) criteria, in the spondyloarthritis (SpA) spectrum, as many patients develop involvement of axial joints, especially the sacroiliac [15, 16].

These definitions are not widely adopted and have not been validated in pediatric-onset IBD (pIBD). Based on the International League of Associations for Rheumatology (ILAR) classification criteria, the pediatric equivalent of adult SpA is enthesitis-related arthritis (ERA), a subtype of juvenile idiopathic arthritis (JIA) [17]. However, arthritis associated with IBD is not comprised within the ILAR criteria for ERA.

Children with IBD and MSK manifestations often experience persistent joint pain and discomfort during follow-up, even under treatment [18]. Articular complaints are identified in some studies as the primary factor contributing to the decline in health-related quality of life [19].

Only a few data are available on the prevalence and characteristics of MSK manifestations in pIBD, and most published cohorts are small and not well defined. Arthritis in pIBD has been recorded in 2.4% to 18.5% of cases and, like for other extra-articular symptoms, its prevalence has been found to be higher in CD than in UC [4, 5, 9, 18, 20–28].

The primary aim of this study was to describe the characteristics of MSK manifestations in pIBD through a nationwide observational study that involved most Italian pediatric rheumatology centers. A further objective was to seek for predictors of persistently active arthritis at year 1 after pIBD diagnosis.

Patients and methods

Study design and patient selection

We conducted a multicenter, retrospective cohort study at 25 centers that are part of the Italian Society of Pediatric Rheumatology (ReumaPed). We included patients who: 1) had a diagnosis of pIBD (CD, UC or IBDU), based on the ensemble of history, physical examination, endoscopic features, histopathologic findings, and radiographic studies, according to the Porto criteria [29]; 2) had the onset of pIBD before the age of 18; 3) had developed MSK manifestations; 4) were seen at each participating center between January 2010 and November 2023; and 5) had at least 1 year of follow-up after pIBD diagnosis. Patients with a prior diagnosis of JIA who later developed pIBD were included.

Assessment of MSK manifestations

The following MSK manifestations were recorded for each patient: arthritis, defined as joint swelling or, if swelling was not present or detectable clinically, as in the case of cervical spine or hip involvement, as the presence

of joint pain or tenderness and limitation of joint movement, persisting for at least 6 weeks, observed by a physician, and not due to primarily mechanical disorders or other non-inflammatory causes; enthesitis, defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone; dactylitis, defined as sausage-like inflammation involving the entire digit, usually in an asymmetric distribution, which extends beyond the joint margin and may be painful; arthralgia, defined as isolated joint pain or tenderness; inflammatory back pain, defined as low back pain with insidious onset, that improves with exercise, is not relieved by rest and occurs predominantly at night [30]. Axial arthritis was defined as the presence of changes typical of sacroiliitis on magnetic resonance imaging (MRI) [31]. Peripheral arthritis was defined as the involvement of any joint except the sacroiliac joint and the spine. Peripheral arthritis was classified based on the number of affected joints as monoarthritis (involving one individual joint), oligoarthritis (involving 2–4 joints), and polyarthritis (involving 5 or more joints).

MSK manifestations could have occurred before, simultaneously with, or after the diagnosis of pIBD, and could have presented either as isolated symptoms or in combination with other clinical features. pIBD diagnosis had to be confirmed by endoscopic evaluation, as defined by Porto criteria.

Other clinical assessments

Family history, demographic information, non-MSK extra-articular symptoms, including fever, skin rash, diarrhea, abdominal pain, weight loss, oral aphthosis, and growth failure, and comorbidities, including uveitis, chronic non-bacterial osteomyelitis (CNO), psoriasis, pyoderma gangrenosum, erythema nodosum, autoimmune hepatitis, and primary sclerosing cholangitis, were recorded for all patients. Laboratory investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), ferritin, albumin, and fecal calprotectin. Clinical and laboratory data were collected at three time points: at first evaluation at study center, at pIBD diagnosis, and at 1-year follow-up visit after pIBD diagnosis. Diagnostic screening for rheumatic disorders included determination of Human Leukocyte Antigen B27 (HLA-B27), antinuclear antibodies (ANA), and rheumatoid factor (RF).

At each study visit, ongoing therapies and the prescription of any new treatments were recorded.

Study outcomes

The primary objective of the study was the characterization of the spectrum of MSK manifestations in the whole cohort of patients with pIBD, and in CD and UC/IBDU separately. A secondary outcome was the identification of potential predictors of arthritis remission at 1 year after pIBD diagnosis. Clinical remission of arthritis was defined as the absence of any evidence of active inflammation in all body joints.

Study data were collected at each participating center through a standardized case report form and were, then, entered in an ad hoc Excel file. The study protocol was approved by the local ethics committee of the coordinating center [ASL Lecce, Italy (codex REUMAPED—28 August 2022)] and of each participating center.

Statistics

Descriptive statistics were reported as medians and interquartile ranges (IQR) for continuous variables, and as absolute frequencies and percentages for categorical variables. Comparisons of disease characteristics between patient groups were performed using the Mann–Whitney U test for continuous data and either the chi-square test or Fisher's Exact test, as appropriate, for categorical data. All statistical tests were two sided, and a p-value of less than 0.05 was considered statistically significant.

Univariable and multivariable analyses were conducted to identify factors associated with active versus inactive arthritis at the 1-year follow-up visit after pIBD diagnosis. Variables with a p-value ≤ 0.20 in univariable analyses, or those considered a priori to be clinically relevant, were included in the multivariable logistic regression model. The outcome of interest was the presence of active arthritis at one-year follow-up. A step-down approach was used, by evaluating systematically the impact of removing variables from the full model. The potential explanatory variables assessed included type of pIBD, time of onset of MSK symptoms, characteristics of joint involvement, extra-articular symptoms, ANA positivity, and therapy administered. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). All the analyses were performed using Jamovi version 2,6 [32].

Results

A total of 180 patients, 111 (61.7%) with CD, 55 (30.5%) with UC, and 14 (7.8%) with IBDU, were included in the study. Demographic features and comorbidities for the entire cohort and for CD and UC/IBDU separately are shown in Table 1.

Fifty-six percent of the patients were female, and the median age at onset of MSK symptoms was 12 years (IQR 9–14.1). Compared to the CD cohort, patients with UC/IBDU tended to be more frequently female (65.2% vs. 51.4%, $P = 0.07$) and showed a slightly younger median age at MSK symptom onset (11.3 vs. 12.3 years, $P = 0.05$). Very early-onset IBD (diagnosed before age 6) was observed in 6.7% of all patients. A family history of IBD and psoriasis was reported in 10.0% and 8.3% of patients, respectively.

Table 1 Baseline demographic features and comorbidities in 180 patients with pIBD and MSK manifestations

	All patients (*n* = 180)	CD (*n* = 111)	UC/IBDU (*n* = 69)	*P* value
Females	102 (56.6)	57 (51.4)	45 (65.2)	0.07[a]
Median (IQR) age at pIBD diagnosis, years	11.5 (9.6—13.6)	12 (10—13.8)	11.3 (8.4—12.75)	0.09[b]
Median (IQR) age at onset of MSK symptoms, years	12 (9—14.1)	12.3 (9.91—14.41)	11.3 (7.13—14.42)	0.05[b]
Very early-onset IBD	12 (6.7)	6 (5.4)	6 (8.7)	0.39[a]
Caucasian ethnicity	169 (93.9)	102/109 (93.6)	67 (97.1)	0.15[a]
Family history of IBD	18 (10.0)	10 (9.0)	8 (11.6)	0.57[a]
Family history of psoriasis	15 (8.3)	9 (8.1)	6 (8.7)	0.89[a]
Comorbidities				
Recurrent oral aphthosis	20 (11.1)	15 (13.5)	5 (7.3)	0.19[a]
Erythema nodosum	11 (6.1)	9 (8.1)	2 (2.9)	0.16[a]
Uveitis	7 (3.9)	4 (3.6)	3 (4.4)	0.80[a]
Pyoderma gangrenosum	2 (1.1)	0	2 (2.9)	0.07[a]
Sclerosing cholangitis	6 (3.3)	1 (0.9)	5 (7.3)	0.021[a]
Autoimmune hepatitis	3 (1.7)	0	3 (4.4)	0.027[a]
Chronic nonbacterial osteomyelitis	10 (5.6)	7 (6.3)	3 (4.4)	0.57[a]
Psoriasis	9 (5.0)	6 (5.4)	3 (4.4)	0.75[a]

Data are expressed as number (%), unless otherwise indicated. *pIBD* pediatric-onset inflammatory bowel disease, *IQR* interquartile range, *MSK* musculoskeletal, *CD* Crohn's disease, *UC* ulcerative colitis, *IBDU* unclassified IBD; very early-onset IBD = age at onset < 6 years

[a] chi-square test; [b]Mann–Whitney U test

Table 2 Characteristics of musculoskeletal manifestations in 180 patients with pIBD

	All patients (*n* = 180)	CD (*n* = 111)	UC/IBDU (*n* = 69)	*P* value
MSK symptoms				
Arthritis	125 (69.4)	74 (66.7)	51 (73.9)	0.30[a]
Arthralgia	131 (72.8)	81 (73.0)	50 (72.5)	0.94[a]
Inflammatory back pain	46 (25.6)	27 (24.3)	19 (27.5)	0.63[a]
Dactylitis	10 (5.6)	4 (3.6)	6 (8.7)	0.15[a]
Enthesitis	20 (11.1)	13 (11.7)	7 (10.1)	0.74[a]
Timing of onset of MSK symptoms				
Median (IQR) interval between pIBD diagnosis and onset of MSK symptoms, months	−1.00 (−12.3; 13.0)	−2 (−11.5; 11.0)	1 (−21.0; 14)	0.62[b]
Before pIBD diagnosis	85 (47.2)	57 (51.4)	28 (40.6)	
Concomitant or after pIBD diagnosis	95 (52.8)	54 (48.7)	41 (59.4)	
Phenotype of arthritis				0.22[a]
Peripheral	96/125 (76.8)	56/74 (75.7)	40/51 (78.4)	
Axial without peripheral involvement	18/125 (14.4)	9/74 (12.2)	9/51 (17.6)	
Axial with peripheral involvement	11/125 (8.8)	9/74 (12.2)	2/51 (3.9)	
Articular pattern				0.41[a]
Monoarthritis	33/125 (26.4)	21/74 (28.4)	12/51 (23.5)	
Oligoarthritis	65/125 (52.0)	40/74 (54.1)	25/51 (49.0)	
Polyarthritis	27/125 (21.6)	13/74 (17.6)	14/51 (27.5)	

Data are expressed as number (%), unless otherwise indicated. *pIBD* pediatric-onset inflammatory bowel disease, *IQR* interquartile range, *MSK* musculoskeletal, *CD* Crohn's disease, *UC* ulcerative colitis, *IBDU* unclassified IBD; concomitant = in the month in which the diagnosis of pIBD was made

[a] chi-square test; [b]Mann–Whitney U test

Oral aphthosis, erythema nodosum, and CNO were reported in both CD and UC/IBDU cohorts, with slightly higher frequencies in patients with CD compared to those with UC/IBDU, though these differences were not statistically significant. In contrast, sclerosing cholangitis, and autoimmune hepatitis were significantly more prevalent among patients with UC/IBDU. Psoriasis was reported in 5% of the total cohort. Uveitis occurred in 3.9% of patients, with no significant difference between CD and UC/IBDU groups, and was equally distributed between acute and chronic forms.

The characteristics of MSK manifestations are summarized in Table 2.

The median interval between the onset of MSK symptoms and pIBD diagnosis was −1.0 month (IQR −12.3 to 13.0). The interval was slightly longer in patients with CD (−2 months, IQR −11.5 to 11.0) compared to those with UC/IBDU (1 month, IQR −21.0 to 14), though this difference was not statistically significant ($p = 0.62$). MSK symptoms were reported to occur before the pIBD diagnosis in 51.4% and 40.6% of CD and UC/IBDU patients, respectively. At the last visit, among 149 evaluable patients, the median follow-up duration after pIBD diagnosis was 54 months (IQR 34–77 months).

The most common MSK manifestations were arthralgia (72.8%), arthritis (69.4%), inflammatory back pain (25.6%), enthesitis (11.1%), and dactylitis (5.6%). Other symptoms at onset of MSK manifestations included fever in 30 (16.7%), skin rash in 6 (3.3%), diarrhea in 45 (25.0%), abdominal pain in 53 (29.4%), weight loss in 38 (21.1%), oral aphthosis in 13 (7.2%), and growth failure in 6 (3.3%) patients of the total cohort.

Eighty-five patients presented with MSK symptoms prior to the diagnosis of pIBD, at a median time of −1.08 months (IQR −3.42; −0.33 months). Many of these patients had symptoms and laboratory values at MSK onset that could have raised the suspicion of IBD. These were: diarrhea in 27/85 (31.8%), abdominal pain in 25/85 (29.4%), weight loss in 19/85 (22.4%), anemia in 3/73

(4.1%), hypoalbuminemia in 17/50 (34.0%), and elevated fecal calprotectin in 36/55 (65.5%).

Of the 125 patients with arthritis, 96 (76.8%) had peripheral arthritis, 18 (14.4%) had axial disease, and 11 (8.8%) had concomitant axial and peripheral joint inflammation. Overall, axial arthritis with or without peripheral arthritis was slightly more frequent in CD (24.4%) than in UC/IBDU (21.5%). The majority of the patients (52.0%) had an oligoarticular pattern, 26.4% had monoarthritis, and 21.6% had polyarthritis. The most frequently affected joints were the knee (44.0%), the ankle (32.0%), the hip (16.0%), the wrist and small hand joints (12.8% each) (Fig. 1).

Table 3 presents the comparison between patients with peripheral arthritis and those with axial arthritis (with or without peripheral joint disease).

The distribution of IBD subtypes was similar between groups. A higher proportion of males was observed in the axial group (62.1% vs. 37.5%, $P = 0.019$). The median age at arthritis onset was significantly higher in patients with axial involvement (14.5 years, IQR 11.0–14.9) compared to those with peripheral arthritis (11.1 years, IQR 7.5–13.4; $P = 0.010$).

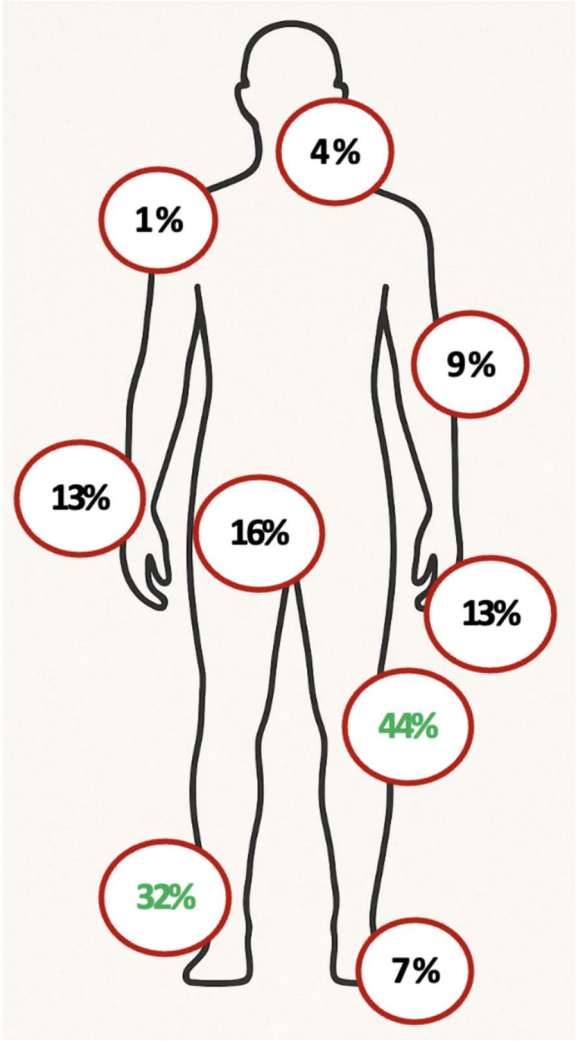

Fig. 1 Frequency of joint involvement in 125 patients with pIBD and arthritis

Arthralgia, dactylitis, and enthesitis were reported in both groups with similar frequencies. Inflammatory back pain was more frequent in the axial group (58.6% vs. 14.6%, $p < 0.001$). The timing of arthritis onset relative to pIBD diagnosis was comparable between groups.

Affected joint patterns differed significantly between the two groups ($P = 0.041$). Oligoarticular arthritis was the most common pattern in both groups, but was more frequent among patients with axial involvement (72.4%) compared to those with peripheral arthritis (45.8%). In contrast, polyarticular and monoarticular patterns were more commonly observed in the peripheral arthritis group (24.0% and 30.2%, respectively) than in the axial group (13.8% for both). Joint involvement also varied, with small hand joints affected more often in the peripheral group (18.0% vs. 0%, $p = 0.032$), and ankle involvement significantly more frequent in the peripheral group (41.6% vs. 13.6%, $p = 0.015$).

Comorbidities, such as uveitis and psoriasis, were observed at similar rates in both groups. The frequency of ANA and HLA-B27 positivity did not differ significantly.

At one-year follow-up, active pIBD and arthritis were present in both groups at comparable rates. Inflammatory back pain and sacroiliitis were significantly more frequent in the axial group ($p < 0.001$ for both). Use of biologic and conventional synthetic DMARDs was similar, but intra-articular glucocorticoid administration (36.5% vs. 13.8%, $p = 0.021$), and systemic glucocorticoids (68.8% vs. 41.4%, $p = 0.008$) were given more commonly in the peripheral group.

Table 4 reports the frequency of the main laboratory features detected at onset of MSK manifestations.

At onset of MSK manifestations, ANA positivity was recorded in 24.1% of patients tested, with similar rates in CD (21.0%) and UC/IBDU (28.8%) groups ($p = 0.30$). HLA-B27 positivity was found in 7.0% of patients overall (4.4% in CD and 11.5% in UC/IBDU, $p = 0.26$). Leukocytosis was detected in 7.8% of patients, with comparable frequencies between CD (8.6%) and UC/IBDU (6.7%) ($p = 0.66$).

Significant differences were observed in markers of inflammation and nutritional status. Low serum albumin was more frequent in CD patients (37.9%) compared to UC/IBDU (10.5%) ($p = 0.003$). Elevated CRP was found in 62.9% of patients overall, with higher prevalence in CD (72.7%) than in UC/IBDU (46.7%) ($p < 0.001$). Similarly, elevated ESR was more common in CD (83.5%) than in UC/IBDU (58.3%) ($p < 0.001$).

Table 3 Comparison between patients with peripheral arthritis and patients with axial with or without peripheral arthritis

	Peripheral arthritis (*n* = 96)	Axial with or without peripheral arthritis (*n* = 29)	*p* value
Demographic and clinical features			
Crohn's disease	56 (58.3)	18 (62.1)	0.72[a]
Ulcerative colitis	31 (32.3)	8 (27.6)	0.63[a]
Unclassified IBD	9 (9.4)	3 (10.3)	0.88[a]
Males	36 (37.5)	18 (62.1)	0.019[a]
Median (IQR) age of arthritis onset, years	11.1 (7.5- 13.4)	14.5 (11.0 −14.9)	0.010 [b]
MSK symptoms			
Arthralgia	62 (64.6)	19 (65.5)	0.93[a]
Dactylitis	7 (7.3)	3 (10.3)	0.59[a]
Enthesitis	10 (10.4)	6 (20.7)	0.15[a]
Inflammatory back pain	14 (14.6)	17 (58.6)	< 0.001[a]
Timing of arthritis onset			0.76[a]
Before pIBD diagnosis	45/84 (53.6)	11/22 (50.0)	
Concomitant or after pIBD diagnosis	39/84 (46.4)	11/22 (50.0)	
Articular pattern			0.041[a]
Oligoarticular	44 (45.8)	21 (72.4)	
Polyarticular	23 (24.0)	4 (13.8)	
Monoarticular	29 (30.2)	4 (13.8)	
Affected joints			
Cervical spine	5/91 (5.5)	0/24	0.24[a]
Shoulder	1/89 (1.1)	0/22	0.62[a]
Elbow	9/89 (10.1)	2/22 (9.1)	0.89[a]
Wrist	15/89 (16.9)	1/22 (4.5)	0.14[a]
Small hand joints	16/89 (18.0)	0/22	0.032[a]
Hip	13/89 (14.6)	7/22 (31.8)	0.06[a]
Knee	48/88 (54.5)	7/22 (31.8)	0.06[a]
Ankle	37/89 (41.6)	3/22 (13.6)	0.015[a]
Small foot joints	9/89 (10.1)	0/22	0.12[a]
Comorbidities			
Uveitis	5 (5.2)	2 (6.9)	0.73[a]
Psoriasis	4 (4.2)	1 (3.4)	0.86[a]
Laboratory tests			
ANA positivity	23/82 (28.0)	3/17 (18.6)	0.37[a]
HLA-B27 positivity	2/37 (5.4)	1/17 (5.9)	0.94[a]
Follow-up 1 year after pIBD diagnosis			
Active pIBD	32/91 (35.2)	12/25 (48.0)	0.24[a]
Active arthritis	22/93 (23.7)	5/24 (20.8)	0.77[a]
Inflammatory back pain	0/88	3/23 (13.0)	< 0.001[a]
Sacroiliitis	2/84 (2.4)	6/24 (25.0)	< 0.001 [a]
Active uveitis	1/92 (1.1)	0/25	0.60 [a]
Therapy during follow-up			
bDMARDs	76 (79.2)	21 (72.4)	0.44 [a]
csDMARDs	69 (71.9)	22 (75.9)	0.67 [a]
Intra-articular glucocorticoids	35 (36.5)	4 (13.8)	0.021 [a]
Systemic glucocorticoids	66 (68.8)	12 (41.4)	0.008[a]

Data are expressed as number (%), unless otherwise indicated. *pIBD* pediatric-onset inflammatory bowel disease, *IQR* interquartile range, *MSK* musculoskeletal; Concomitant = in the course of the month in which the diagnosis of p-IBD was made, *ANA* antinuclear antibodies, *HLA-B27* human leukocyte antigen B27, *bDMARDs* biologic disease-modifying antirheumatic drugs, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs

[a]chi-square test; [b]Mann–Whitney U test

Table 4 Laboratory tests at onset of MSK manifestations in 180 patients with pIBD

	All patients (*n* = 180)	CD (*n* = 111)	UC/IBDU (*n* = 69)	*P* value
ANA positivity	32/133 (24.1)	17/81 (21.0)	15/52 (28.8)	0.30[a]
HLAB-27 positivity	5/71 (7.0)	2/45 (4.4)	3/26 (11.5)	0.26[a]
Leukocytosis	12/153 (7.8)	8/93 (8.6)	4/60 (6.7)	0.66 [a]
Low serum albumin	29/104 (27.9)	25/66 (37.9)	4/38 (10.5)	0.003[a]
Elevated CRP	100/159 (62.9)	72/99 (72.7)	28/60 (46.7)	< 0.001[a]
Elevated ESR	116/157 (73.9)	81/97 (83.5)	35/60 (58.3)	< 0.001[a]
Anemia	23/155 (14.8)	11/94 (11.7)	12/61 (19.7)	0.17[a]
Elevated ferritin	8/113 (7.1)	7/75 (9.3)	1/38 (2.6)	0.19[a]
Elevated fecal calprotectin	74/123 (60.1)	53/76 (69.7)	21/47 (44.7)	0.006[a]
Low ferritin	36/113 (31.9)	22/75 (29.3)	14/38 (36.8)	0.42[a]

Data are expressed as number (%). Anti-nuclear antibodies (ANA) were defined as positive if titer was ≥ 1:160 on indirect immunofluorescence; HLA-B27 = human leukocyte antigen B27; leukocytosis = WBC > 14×10^9/L; low serum albumin = < 3,5 g/dl; elevated erythrocyte sedimentation rate (ESR) = > 20 mm/1st hour; elevated C-reactive protein (CRP) = > 1 mg/dl; anemia = < 11.5 gr/dl; elevated ferritin = > 200 ng/ml; elevated fecal calprotectin = > 250 mg/Kg; low ferritin = value below to the lower limits of the local laboratory

[a] chi-square test

Anemia was reported in 14.8% of patients, with a slightly higher frequency in UC/IBDU (19.7%) compared to CD (11.7%) ($p = 0.173$). Elevated ferritin was noted in a small proportion of patients (7.1%).

At first rheumatology visit, 22.3% of patients received intra-articular glucocorticoids, 42.9% conventional synthetic DMARDs (csDMARDs), 37.3% biologic DMARDs (bDMARDs), and 21.7% systemic glucocorticoids. At pIBD diagnosis, systemic glucocorticoids or csDMARDs were prescribed in approximately half of the patients, and bDMARDs in about one third. During follow-up, there was a progressive decrease in the use of intra-articular glucocorticoids (1.2% at one year and 0% at last follow-up visit) and systemic glucocorticoids (13.8% at one year, 5.8% at last follow-up visit). In contrast, the frequency of bDMARDs administration increased steadily, reaching 72.5% at last follow-up observation. The cumulative frequency of administration was 22.2% for intra-articular glucocorticoids, 62.8% for systemic glucocorticoids, 70.0% for csDMARDs, and 79.4% for bDMARDs. Eleven (12.9%) of the 85 patients with MSK symptoms preceding the diagnosis of pIBD were on bDMARDs at the time of pIBD diagnosis (see Additional file 1 for details of medication exposure at different time points).

At one-year follow-up visit after pIBD diagnosis, 23% of the 125 patients with arthritis had persistently active inflammation in one or more joints, and 37.9% had ongoing IBD activity. On univariable analysis, patients with persistently active arthritis at one-year follow-up had more frequently a positive ANA status (45.8% vs 19.7%, $p = 0.012$) and involvement of small foot joints (20.0% vs 5.0%, p = 0.019), and were more commonly receiving csDMARDs (93% vs 71.4%, $p = 0.025$) compared to those with non-active arthritis There were no significant differences in gender, type of underlying gut disease, or articular pattern between the groups. (see Additional file 2).

ANA positivity (OR = 3.05, 95% CI: 1.05–8.89), and a polyarticular course of arthritis (OR = 3.42, 95% CI: 1.13–10.38) were independently associated with persistence of active arthritis at 1 year after pIBD diagnosis on multivariable analysis (Table 5).

Discussion

We present herein the results of the GASTROREUM study, a multicenter survey of MSK manifestations in patients with pIBD followed at the centers belonging to the Italian Society of Pediatric Rheumatology. Owing to the large size of the patient population and number of participating centers, our sample is likely representative of the whole patients with this clinical phenotype seen in Italian pediatric rheumatology clinics.

Most epidemiological studies in pIBD found a slight male predominance among patients with CD, whereas UC is usually characterized by a more balanced gender ratio [33, 34]. Our finding of an equal gender distribution in patients with CD and a predominance of females in those with UC/IBDU suggests an overall tendency for MSK manifestations to prevail in female patients, in line with the female predilection seen in most forms of JIA. However, in axial arthritis, there was a male predominance (62%), as typically seen in ERA/juvenile SpA [35].

The median age at pIBD diagnosis in our cohort (11.5 years) is comparable to that recorded in other series, with or without MSK manifestations [4, 5, 28, 36]. Unlike other studies, our patients with UC/IBDU were, on average, younger at diagnosis than those with CD, although the difference was not statistically significant [5].

The group of patients in whom MSK symptoms occurred before the diagnosis of pIBD is of particular clinical relevance, as the onset of arthritis before gastrointestinal symptoms may lead to misdiagnose JIA and to overlook bowel involvement. This phenomenon was noticed in as many as 47% of the patients and was more frequent among those with CD. In other reported series of pIBD the frequency of arthritis preceding IBD diagnosis is widely variable, from 3.9% to 30% [4, 5, 18, 25, 26, 28]. This disparity may be explained by differences in study design, patient characteristics, definition of MSK manifestations (e.g. arthritis vs arthralgia), and specialty setting (e.g. rheumatology vs gastroenterology).

Studies based on multinational registries have investigated the development of intestinal inflammation among patients with JIA. An incidence of IBD of 1.31 per 1000 patient-year, irrespective of ongoing bDMARD therapy, was reported, which contrasts with the incidence of IBD

Table 5 Univariable and multivariable models for predicting active arthritis at 1 year after pIBD diagnosis

	Univariable (*N* = 119)				Multivariable (*N* = 85)			
Effect	**OR**	**95%CI**		***p*-value**	**OR**	**95%CI**		***p*-value**
Female	**0.94**	**0.39**	**2.24**	**0.880**				
Ulcerative colitis	0.79	0.31	2.00	0.619				
Chron's disease	1.02	0.43	2.45	0.958				
Unclassified IBD	1.52	0.37	6.32	0.566				
Onset of MSK symptoms after pIBD diagnosis	1.52	0.64	3.63	0.346				
Onset of MSK symptoms before pIBD diagnosis	0.66	0.28	1.57	0.346				
ANA positivity	3.45	1.28	9.30	0.015	3.05	1.05	8.89	0.041
Joints involved								
Hip	0.83	0.25	2.76	0.756				
Ankle	1.92	0.77	4.78	0.163				
Knee	1.54	0.62	3.84	0.356				
Elbow	1.42	0.34	5.97	0.630				
Small hand joints	2.21	0.71	6.86	0.170				
Small foot joints	4.75	1.17	19.34	0.030				
Wrist	1.57	0.49	5.05	0.450				
Cervical spine	0.83	0.09	7.81	0.873				
Shoulder	9.97	0.10	955.83	0.323				
Polyarticular arthritis	2.06	0.79	5.32	0.138	3.42	1.13	10.38	0.030
Location				0.957				
Axial arthritis without peripheral involvement vs peripheral arthritis	0.83	0.23	3.07					
Combined axial and peripheral arthritis vs peripheral arthritis	1.07	0.22	5.22					
MSK symptoms								
Sacroiliac joint tenderness	0.81	0.29	2.24	0.685				
Inflammatory back pain	0.81	0.29	2.24	0.685				
Enthesitis	0.21	0.03	1.71	0.146				
Lower back stiffness	0.83	0.25	2.72	0.753				
Sacroiliitis	0.87	0.37	2.07	0.757				
Therapy (ever exposed to)								
Systemic glucocorticoids	2.25	0.83	6.11	0.112				
bDMARDs	0.74	0.26	2.12	0.571				
csDMARDs	4.92	1.09	22.29	0.039				
IAGs	2.14	0.88	5.21	0.092				
Other extra-articular manifestations								
Recurrent oral aphthosis	0.83	0.22	3.20	0.791				
Erythema nodosum	0.84	0.17	4.21	0.832				
Uveitis	0.24	0.01	5.57	0.375				
Pyoderma gangrenosum	1.14	0.01	104.24	0.954				
Sclerosing colangitis	1.12	0.11	11.18	0.926				
Autoimmune hepatitis	10.46	0.10	> 999	0.317				
CNO	1.13	0.01	103.14	0.959				
Psoriasis	5.62	0.89	35.59	0.067				

in the general population of 0.23 per 1000 person-years [37, 38]. The PHARMACHILD registry found a prevalence of 0.54% of newly diagnosed IBD in JIA patients [39]. Gut inflammation was associated with the ERA subtype and the use of etanercept. A similar observation was disclosed in the BiKeR registry [40]. It has been postulated that JIA patients may be more likely to experience the overt onset of a pre-existing clinically silent IBD while receiving etanercept because this medication is ineffective in CD [41]. Conversely, switching from etanercept to adalimumab may prevent symptomatic IBD. In the PHARMACHILD registry, 48% of JIA patients with subsequent IBD were exposed to etanercept in the three months preceding onset of intestinal inflammation [39]. However, only 13% of our patients with MSK symptoms preceding pIBD diagnosis were receiving bDMARDs.

A sizeable proportion of our patients with MSK symptoms preceding pIBD diagnosis experienced diarrhea

(31.8%) and abdominal pain (29.4%) before the recognition of the intestinal illness. The high prevalence of these symptoms is partly explained by their frequent occurrence shortly before pIBD diagnosis. Nonetheless, this observation highlights the importance of paying attention to gastrointestinal symptoms in patients with arthritis. Levy and co-workers reported that 78.2% of patients with arthritis occurring before pIBD diagnosis had a prolonged history of one or more gastrointestinal symptoms [26].

Arthralgia was the most prevalent MSK manifestation in our cohort (72.9%), in line with the findings of other studies [22, 24, 42]. Arthritis ranked second (69.4%), and presented most often with peripheral joint involvement and oligoarticular pattern. The knee and the ankle were the most frequently affected joints, similar to what reported in other studies in pIBD [18, 20, 22, 26].

Our definition of axial arthritis was restricted to MRI-confirmed sacroiliitis, a choice based on the guidelines for the management of extra-articular manifestations in adult-onset IBD, and on recent studies in pIBD [3, 18]. Axial arthritis, as defined above, with or without peripheral arthritis, was observed in 23.2% of our patients, while the prevalence of inflammatory back pain was 25.6%. Seventy-six of the patients with inflammatory back pain underwent MRI, which confirmed sacroiliitis in only half of the cases. In both pediatric and adult IBD, axial arthritis is less frequent than peripheral arthritis. In our cohort, the peripheral-to-axial arthritis ratio was 3.3:1, consistent with most pediatric studies. [4, 5, 18, 20, 25, 28, 42–44].

Enthesitis is a key feature of ERA/juvenileSpA [17, 30]. Its occurrence has been seldom evaluated in previous studies of pIBD. In a cross-sectional analysis, Gerenli and Sozeri found that 45% of pIBD patients had at least one tender enthesis, whereas Horton et al. reported a lower prevalence (21%) [23, 45]. Lower rates of enthesitis (18.1% vs. 44.3%), and dactylitis (4.5% vs. 17.4%) were observed in adult patients with IBD-associated SpA than in those with SpA alone [46]. Enthesitis and dactylitis were relatively uncommon in our cohort, with a prevalence of 11.1% and 5.6% respectively, similar to that observed in the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) IBD registry cohort [28].

Uveitis affects approximately 5% of adults with IBD, but its prevalence in pIBD is less established, with estimates ranging from 0.62% to 1.82%, suggesting a lower prevalence than in adults [5, 47, 48]. Uveitis was detected in 3.9% of our patients with pIBD and MSK symptoms, with a higher frequency in ANA-positive cases (9.4%), and a balanced distribution between acute and chronic subtypes.

The high frequency of ANA detected in our patients with pIBD and arthritis (24%) is noteworthy, as these autoantibodies are not part of the typical laboratory abnormalities of IBD. This finding may partly reflect the high frequency of the early-onset ANA-positive subset in Italian children with JIA [49]. These patients typically have an early age of disease onset. Although average age at onset of our pIBD patients was 10 years, the association of pIBD-related arthritis with a positive ANA status has not been reported previously and deserves further investigations in patient populations seen in different geographic settings. The high onset age of our patients with pIBD is more aligned with ERA, which tends to occur in older children [50]. However, ERA is typically marked by male predilection [35], whereas 56.6% of our patients with pIBD-associated arthritis were girls.

The 7% prevalence of HLA-B27 observed in our cohort falls within the range reported for adult IBD patients in European studies [46, 51]. Among children with CD, HLA-B27 positivity was identified in 10% and 11% of those with axial and peripheral arthritis, respectively [19].

In our cohort, approximately one-quarter of patients with arthritis experienced persistently active joint disease at one year. This rate was lower than that observed in the Italian SIGENP IBD Registry cohort, where 36% of patients had persistent active arthritis [28]. We found that ANA positivity and a polyarticular disease course were risk factors for ongoing arthritis activity after one year on multivariable analysis. A polyarticular disease phenotype, as opposed to oligoarthritis, is a well-known indicator of worse prognosis in JIA [52]. Although ANA positivity in JIA is linked to an increased risk of uveitis, its correlation with articular outcome is unclear [53, 54]. The prognostic role of ANA in pIBD with MSK manifestations should be further explored in other patient populations.

In our patient sample, bDMARDs represented the primary long-term treatment modality. There was a clear trend towards a reduced use of systemic glucocorticoids, which dropped from 48.6% to 5.8% during follow-up, while the administration of bDMARDs increased to 72.5%.

Our study is limited by its retrospective design, that hindered our ability to identify precisely certain clinical variables and to obtain complete laboratory data for all patients. The lack of control groups of patients with pIBD without MSK manifestations and of patients with arthritis and no IBD did not allow us to obtain insights into the distinctive features of patients with pIBD and MSK symptoms. Because all patients were followed in pediatric rheumatology settings, we cannot exclude that those seen primarily by pediatric gastroenterologists could have different clinical characteristics. In addition,

detailed information on the timing and indication of bDMARD initiation relative to the onset of joint and gut inflammation was not consistently available, preventing more in-depth analysis of treatment patterns. The main strength of our study lies in the large size of the patient sample and in the detailed assessment of MSK features.

In summary, our analysis provides a comprehensive characterization of MSK manifestations in patients with pIBD. An important observation was that most patients presented with peripheral arthritis and that a sizeable proportion of them had ANA-positive oligoarthritis, a condition which has not previously associated with pIBD. Our findings confirm that joint symptoms often precede the diagnosis of pIBD, leading to the risk of misdiagnosis as JIA. This observation highlights the need for well-established recommendations that aid to recognize IBD timely in patients who present with articular complaints. That around one quarter of patients still had active arthritis one year after diagnosis despite the widespread use of bDMARDs is a matter of concern and underscores the need for better protocols for the treatment of joint disease, particularly in patients with polyarthritis and a positive ANA status, who carry the highest risk for a refractory course of articular inflammation.

Abbreviations

ANA	antinuclear antibody
ASAS	Assessment of Spondyloarthritis International Society
CD	Crohn's disease
CNO	chronic non-bacterial osteomyelitis
DMARDs	disease-modifying antirheumatic drugs
ERA	enthesitis-related arthritis
IBD	inflammatory bowel diseases
IBDU	unclassified Inflammatory bowel diseases
ILAR	International League of Associations for Rheumatology
JIA	juvenile idiopathic arthritis
MSK	musculoskeletal
pIBD	pediatric onset inflammatory bowel diseases
SpA	spondyloarthritis
UC	ulcerative colitis

Supplementary Information

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Additional file 1.

Additional file 2.

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Authors' contributions

Conceptualization: AC, FD, AR Methodology: AC, FD, AR, MT Formal analysis: AC, MT, SG, RGr, FB Investigation: AC, FD, RGa, MG, SMM, DM, GS, GC, EDG, GF, FC, AMi, SP, FLT, BL, AMa, LM, PB, ANO, GV, MCM, IF, SC, LC, ES, MC, SA, GT, SG, RGr Writing—Original Draft: AC, FD, FB, AR Writing—Review & Editing: AC, FD, RGa, MG, SMM, DM, GS, GC, EDG, GF, FC, AMi, SP, FLT, BL, AMa, LM, PB, ANO, GV, MCM, IF, SC, LC, ES, MC, SA, GT, MT, SG, RGr, FDB, FB, AR All authors reviewed the results and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of [ASL Lecce, Italy (codex REUMAPED—28 August 2022)].

Consent for publication

Written informed consent was obtained from all participants and/or their legal guardians prior to enrollment.

Competing interests

Co-Editor-in-Chief Angelo Ravelli is on the author list.

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