



# The Challenge of IBD-Related Arthritis Screening Questionnaires in Early and Predominantly Enthesal Phenotypes

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Received: April 10, 2024 / Accepted: July 29, 2024  
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## ABSTRACT

**Introduction:** Inflammatory bowel disease (IBD)-related arthritis is recognized as the most prevalent extraintestinal manifestation (EIM) of IBD. The objective of this study was to determine the prevalence and characteristics of undiagnosed IBD-related arthritis and to compare two screening questionnaires, DETection of Arthritis in Inflammatory boweL diseases (DETAIL) and IBd Identification of Spondyloarthritis Questionnaire (IBIS-q), for early disease detection.

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**Methods:** Between April and October 2023, both the DETAIL and IBIS-q questionnaires were administered to consecutive IBD outpatients visiting the University Hospital of Udine, Italy. During routine gastroenterology evaluations, patients aged > 18 years with Crohn's disease (CD) or ulcerative colitis (UC) were requested to complete both questionnaires. Subsequently, all patients who completed the questionnaires underwent a blinded rheumatological evaluation within 2 weeks. Patients with a previous diagnosis of IBD-related SpA were then excluded. **Results:** Overall, 203 patients were enrolled, of whom 26 were excluded because of a prior diagnosis of inflammatory arthritis. Among the remaining 177 patients, 10/177 (5.6%) received a new diagnosis of IBD-related arthritis. The

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median duration of symptoms before diagnosis was 4 (IQR 1.8–10.5) months. Imaging-confirmed enthesitis was the predominant pattern in 8 out of 10 cases (80%, with 8 out of 8 lacking concomitant peripheral arthritis), axial involvement in 1 out of 10 cases (10%), and peripheral arthritis in 1 out of 10 cases (10%). The DETAIL questionnaire exhibited higher specificity, but lower sensitivity compared to the IBIS-q, with a sensitivity of 40.0% (12.2–73.8) and specificity of 84.4% (78.0–89.6) versus a sensitivity of 70.0% (34.8–93.3) and specificity of 74.3% (66.9–80.7). Both questionnaires performed less effectively than in other studies.

**Conclusion:** This study highlights a significant proportion of undiagnosed IBD-related arthritis (5.6%). Enthesitis emerged as the predominant pattern of newly diagnosed arthritis in our cohort, likely due to the recent onset of symptoms. Our study underscores the importance of enthesal involvement in early IBD-related arthritis and the importance of incorporating enthesal involvement into screening questionnaires.

**Keywords:** Arthritis; Inflammatory bowel disease; Screening; Questionnaire; IBD-related arthritis

### Key Summary Points

#### *Why carry out this study?*

Inflammatory bowel disease (IBD)-related arthritis is the most frequent extraintestinal manifestation, affecting approximately 10–39% of individuals with IBD.

Identifying joint involvement, particularly in the early phases of the musculoskeletal disease, enables the utilization of drugs effective for both gut and joint, facilitating comprehensive disease management.

This study aimed to ascertain the prevalence of undiagnosed IBD-related arthritis and to evaluate the efficacy of two screening questionnaires for arthritis within a cohort of patients with IBD.

#### *What was learned from the study?*

This study identified a significant proportion (i.e., 5.6%) of new early diagnoses of arthritis among patients with IBD. The majority of newly identified cases of IBD-related arthritis displayed an enthesal involvement despite the absence of peripheral swelling.

Our results emphasized the importance of questions about enthesal domains to enhance the sensitivity of screening questionnaires, particularly for the detection of early forms of joint disease.

## INTRODUCTION

Inflammatory bowel disease (IBD) is a systemic condition affecting the gastrointestinal tract. Extraintestinal manifestations (EIMs) occur in up to 50% of patients with IBD [1], encompassing conditions such as arthritis, skin and eye diseases (e.g., erythema nodosum, pyoderma gangrenosum, uveitis, and episcleritis), involvement of the hepatobiliary system (e.g., sclerosing cholangitis), and metabolic bone disorders.

Arthritis is the most common EIM, occurring in approximately 10–39% of patients with IBD [2], known as IBD-related arthritis, and usually manifests after the diagnosis of IBD [3].

IBD-related arthritis falls within spondyloarthritis (SpA) and shares key pathogenetic and clinical components. The spectrum of joint involvement ranges from isolated axial disease, meeting radiographic or non-radiographic Assessment of SpondyloArthritis international Society (ASAS) [4] criteria, to pure peripheral disease characterized by arthritis, enthesitis, dactylitis, or a combination of axial and peripheral symptoms [5]. Among them, entheses are a primary site of inflammation and pathology, with axial and peripheral sites involved [6, 7].

Despite the established association and the availability of advanced diagnostic techniques such as magnetic resonance imaging (MRI) and ultrasound (US) [8], there remains a diagnostic delay of around 5–10 years, particularly for axial disease [9, 10]. This delay may be attributed to a lack of multidisciplinary approaches and delayed rheumatological assessments [11]. The prolonged diagnostic delay may increase the risk of disability and decrease the quality of life, while early detection of IBD-related arthritis allows for timely intervention with medications effective for both gut and joint symptoms [12, 13].

Recently, two screening questionnaires, namely DETection of Arthritis in Inflammatory boweL diseases (DETAIL) [14] and IBd Identification of Spondyloarthritis Questionnaire (IBIS-q) [15], have been developed to facilitate the early detection of arthritis among patients with IBD. DETAIL recently underwent validation in a multicenter study, while IBIS-q still requires validation.

The objectives of this study are twofold: first, to determine the prevalence of undiagnosed IBD-related arthritis and describe its clinical phenotype; and second, to assess the effectiveness of IBIS-q and DETAIL as screening tools.

## METHODS

### Patients

The study included a group of patients with IBD who visited the IBD outpatient department at the Hospital of Udine, Italy, from April 2023 to October 2023. As part of their routine gastroenterology assessment, patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) were requested to complete both the DETAIL and IBIS-q questionnaires (Table 1). According to the literature, questionnaires were considered positive with a cutoff of  $\geq 3$  positive answers [14, 15].

Patients with a previous diagnosis of inflammatory arthritis or other inflammatory rheumatic musculoskeletal diseases (RMDs), those under the age of 18, and patients who did not

speak Italian were excluded from participating in the study. Following this, all patients were referred to a rheumatologist for a blinded evaluation within 2 weeks. Informed consent was obtained from each patient in accordance with the Declaration of Helsinki and with local guidelines for good clinical practice. Ethical approvals for the study were obtained (University of Udine, IRB 97/2023).

### Gastroenterological Evaluation

Patients were consecutively enrolled during the routine gastroenterological assessment. Initially, the patient's medical history was collected, including the latest evidence of ileocolonoscopy, in which the concomitant IBD disease activity was described using the Simple Endoscopic Score for Crohn's Disease (SES-CD) [16] for CD and the Mayo Endoscopic Score for Ulcerative Colitis (MAYO) [17] for UC. During the visit, an evaluation of symptoms was performed, considering the presence of diarrhea with stool frequency and the presence of blood and mucus in the stool. Other symptoms assessed included nocturnal symptoms, abdominal pain, fecal urgency and/or incontinence, presence of vomit and fever. Afterwards, the examination was completed by objective assessment of the abdominal and, in selected cases, performing a rectal examination. At the end of the visit, the DETAIL and IBIS-q questionnaires were administered under the supervision of the doctor.

### Rheumatological Evaluation

During the rheumatological examination, 68 tender (TJC) and 66 swollen (SJC) joint counts, Leeds Enthesitis index (LEI), and Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC) were assessed in all patients, while cervical rotation, tragus-to-wall distance, modified Schober's test, and intermalleolar distance were assessed only when axial symptoms were present.

The medical assessment was complemented by US evaluation, driven by physical examination, to assist the IBD-related arthritis diagnosis, mainly to evaluate the enthesal involvement

**Table 1** DETAIL and IBIS-q questionnaires

## DETAIL questionnaire

1. Have you ever had pain and swelling in your finger or toe joint and/or any joint for no other known reason?
2. Do your fingers or toes look swollen and sausage-like?
3. Do you have pain in your heels?
4. Have you ever had low back pain lasting at least 3 months without any trauma?
5. Do you have low back pain that improves with exercise in the morning and/or after rest?
6. Do you wake up at night because of back pain?

## IBIS-q (IBD Identification of Spondyloarthritis Questionnaire)

1. Have you had pain in your heels?
2. Have you ever had back pain lasting at least 3 months that was not injury related?
3. Have you ever had a swollen wrist without having any trauma?
4. Do you wake up at night and walk because of low back pain?
5. In the morning is your back stiff for more than 30 min?
6. Have you ever had a stiff neck for some weeks or months?
7. Have you ever had a pain in your thigh which goes down to your knee and not beyond?
8. Is it difficult to pick things up from the floor without flexing your knees?
9. Have you ever had a swollen finger like a “sausage” for some days?
10. Do you find it difficult to fasten your laces?
11. Do you find it difficult to button your shirt?
12. Do you find it difficult to walk because of foot pain?
13. Have you ever had swollen and painful hands?
14. Have you ever had swollen and painful feet?

The questionnaires are positive if  $\geq 3$  items are checked

or in the case of suspected synovitis at the clinical examination [18, 19]. Furthermore, patients complaining of inflammatory axial symptoms were evaluated with MRI and/or X-ray.

### Case Definition of IBD-Related Arthritis

IBD-related arthritis was defined as fulfillment of ASAS criteria for axial and peripheral involvement [4, 20] and the presence of inflammatory musculoskeletal involvement diagnosed by an experienced rheumatologist (AZ) according to symptom history and the following definitions:

- (i) Arthritis as defined by joint swelling
- (ii) Enthesitis based on tenderness of the enthesis with or without presence of swelling at the enthesial site plus sonographic evidence of active enthesitis according to OMERACT definition, i.e., power Doppler at the enthesis grade  $\geq 1$  plus enthesial thickening and/or hypoechoic areas [21, 22]
- (iii) Dactylitis as determined by clinical examination
- (iv) Axial involvement as determined by inflammatory back pain and radiographic/MRI evidence of sacroiliitis or spondylitis

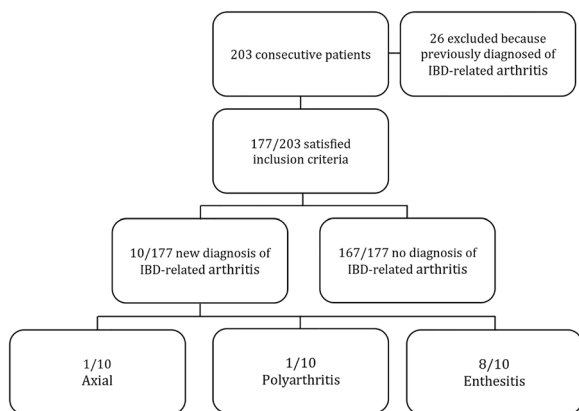
Other conditions mimicking SpA have been assessed according to clinical suspicion and practice by the rheumatologist.

### Statistical Analysis

The baseline demographic and clinical traits of all patients were recorded and inputted into an anonymous database (RedCap). Sensitivity and specificity were computed for both screening tools. Subsequently, the performance of DETAIL and IBIS-q was evaluated by determining the post-test probability of disease using positive (LR+) and negative (LR-) likelihood ratios.

## RESULTS

A total of 203 consecutive patients with IBD were recruited, with 26 individuals being excluded from the study because of a previous diagnosis of SpA or other RMDs. The remaining 177 out of 203 participants who completed the DETAIL and IBIS-q questionnaires were enrolled in the study (Fig. 1). Out of the 177 patients, 92 (52.0%) had UC and 85 (48.0%) had CD. The mean age was 48.4 years (standard deviation (SD)  $\pm$  17.2), and 73 (41.2%) were female. The mean duration of IBD was 8.2 years (SD  $\pm$  5.9). Patient features, including ongoing therapies, are summarized in Table 2.



**Fig. 1** Flowchart of patients enrolled in the study. *IBD* inflammatory bowel disease

### Prevalence and Clinical Phenotypes of Newly Diagnosed IBD-Related Arthritis

In 10 out of 177 patients (5.6%), a new diagnosis of IBD-related arthritis was established, and all patients fulfilled the ASAS criteria for axial or peripheral SpA, based on clinical involvement. The median duration of musculoskeletal symptoms before the diagnosis of IBD-related arthritis was 4 months (IQR 1.8–10.5) (Table 3).

Imaging-confirmed entesitis was the predominant pattern in 8 out of 10 cases axial involvement in 1 out of 10 cases, and peripheral arthritis in 1 out of 10 cases (Fig. 1).

The median LEI and SPARCC were 1 (IQR 1–2) and 2 (IQR 1–3), respectively.

Among the 8 cases with imaging-confirmed entesitis as predominant pattern, 8 out of 8 lacking concomitant peripheral synovitis but in 2/8 (25%) enthesal swelling was present, the mean CRP was 0.6 (+0.4) mg/dl, the mean morning stiffness was 21.0 (+24.9) mins, and the median number of imaging active enthesal sites was 2 (IQR 1–3). The most frequent enthesal site involved was lateral epicondyle of the humerus, followed by Achilles tendon and quadriceps tendon (Fig. 2).

CD was the main IBD pattern in this group of patients (7/10 cases). The endoscopic disease activity measured by SES-CD for CD and MAYO for UC revealed that 5/10 (50%) patients exhibited remission at the rheumatological evaluation, 1 presented mild disease activity, and 4 presented at least moderate disease activity.

Seven out of 10 newly diagnosed patients with IBD-related arthritis were not concomitantly treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biologic disease-modifying antirheumatic drugs (bDMARDs) for IBD during the rheumatological assessment. None of the newly diagnosed patients with IBD-related arthritis were receiving vedolizumab [23].

**Table 2** Demographic features

	Patients that satisfied study criteria ( <i>n</i> = 177)
Age (years), mean ( $\pm$ SD)	48.4 ( $\pm$ 17.2)
Female, <i>n</i> (%)	73 (41.2%)
BMI, mean ( $\pm$ SD)	24.6 ( $\pm$ 2.3)
Smoker, <i>n</i> (%)	39 (22.0%)
Disease duration (years), mean ( $\pm$ SD)	8.2 ( $\pm$ 5.9)
UC, <i>n</i> (%)	92/177 (52.0%)
CD, <i>n</i> (%)	85/177 (48.0%)
Disease location, <i>n</i> (%)	
L1	69/177 (39.0%)
L2	26/177 (14.7%)
L3	78/177 (44.0%)
L4	3/177 (1.7%)
L1 + L2 + L3 + L4	1/177 (0.6%)
Current medication with bDMARD, <i>n</i> (%)	106/177 (59.9%)
TNF inhibitors	66/177 (37.3%)
IL-12/23 inhibitors	13/177 (7.3%)
$\alpha$ 4 $\beta$ 7 integrin antibody	27/177 (15.3%)

*SD* standard deviation, *UC* ulcerative colitis, *CD* Crohn's disease, *IC* indeterminate colitis, *L1* ileitis, *L2* colitis, *L3* ileocolitis, *L4* involvement of the upper digestive tract, *bDMARD* biological disease-modifying antirheumatic drugs, *TNF* tumor necrosis factor, *IL-12/23* interleukin-12/-23

### Comparison of DETAIL and IBIS-q Performance

Among the 177 patients surveyed, 55 individuals (31.1%) showed positive results in either the DETAIL or IBIS-q questionnaires. Specifically, 5 patients (9%) tested positive solely in the DETAIL questionnaire, 26 patients (47.3%) were positive only in the IBIS-q, and 24 patients (43.7%) tested positive in both questionnaires.

Within the remaining 122/177 patients with a negative questionnaire, 29 (16.4%) exhibited a score of 2 for both DETAIL and IBIS-q; while

a score of 1 was present in 36/177 (20.3%) and 32/177 patients (18.1%) in DETAIL and IBIS-q, respectively; ultimately no positive answers were present in 83/177 (46.9%) for DETAIL and 66/177 (37.2%) for IBIS-q.

The DETAIL questionnaire demonstrated a sensitivity of 40.0% (95% CI 12.2–73.8%) and a specificity of 84.4% (95% CI 78.0–89.6%) for diagnosing IBD-related arthritis, yielding a LR+ of 2.6 and a LR– of 0.7 (Table 4). On the other hand, the IBIS-q questionnaire (using a cutoff of  $\geq$  3) exhibited a sensitivity of 70.0% (95% CI 34.8–93.3%) and a specificity of 74.3% (95% CI 66.9–80.7%), with a LR+ of 2.7 and a LR– of 0.4 (Table 4).

**Table 3** Characteristics of newly diagnosed IBD-related arthritis

Patients, <i>n</i>	10
Age (years), mean ( $\pm$ SD)	44.5 ( $\pm$ 12.1)
Male, <i>n</i> (%)	6 (60%)
IBD location, <i>n</i> (%)	
UC	3 (30%)
CD	7 (70%)
IBD activity <sup>a</sup> , <i>n</i> (%)	
Inactive	5 (50%)
Mild	1 (10%)
Moderate	1 (10%)
Severe	3 (30%)
Diagnostic delay (months), median (Q1–Q3)	4 (1.8–10.5)
Patients on immunosuppressive therapy at SpA onset, <i>n</i> (%)	3 (30%)
Patients who have been started on immunosuppressive therapy, <i>n</i> (%)	6 (60%)
SpA phenotype, <i>n</i> (%)	
Axial SpA	1 (10%)
Peripheral SpA	1 (10%)
Enthesitis SpA	8 (80%)

*SD* standard deviation, *IBD* inflammatory bowel disease, *UC* ulcerative colitis, *CD* Crohn's disease, *IC* indeterminate colitis, *SpA* spondyloarthritis

<sup>a</sup>Activity Index assessed using the MAYO for UC and SC scores for CD

### Alternative Diagnoses in False Positive Cases

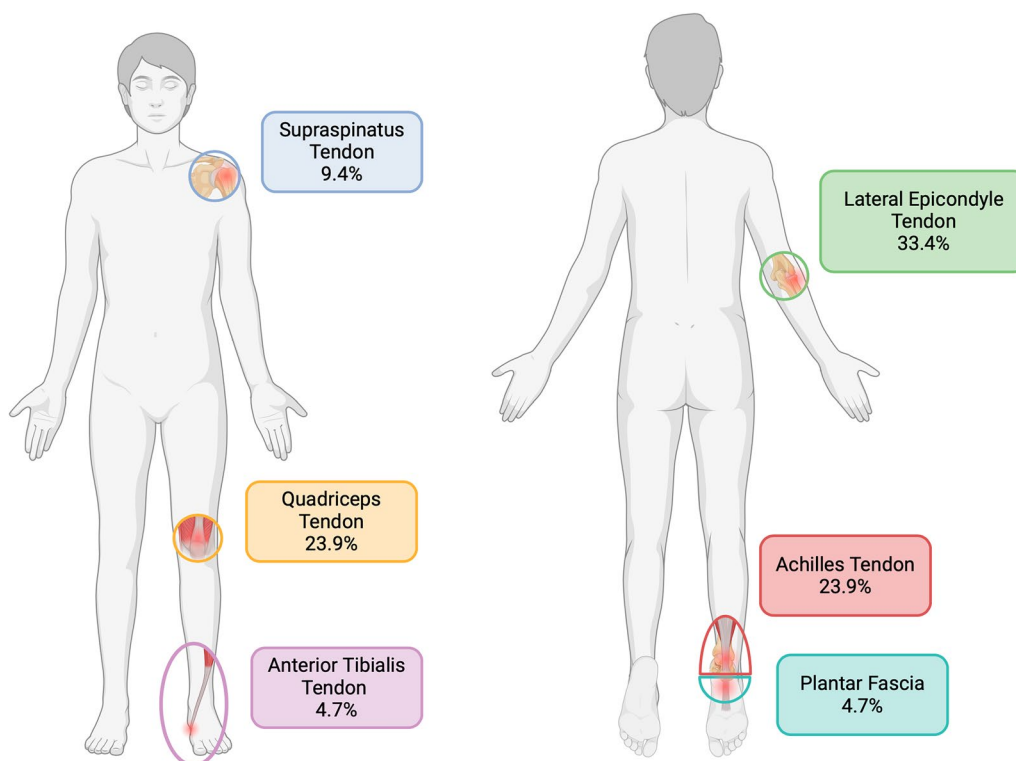
Of 177 patients, 48 presented at least one positive questionnaire (cutoff score  $\geq$  3) without IBD-related arthritis diagnosis. The alternative diagnoses were osteoarthritis in 27 out of 48 cases (56.6%), followed by not otherwise specified arthralgia in 10 out of 48 cases (20.1%), fibromyalgia in 6 out of 48 cases (12.5%),

myofascial pain in 3 out of 48 cases (6.25%), and non-inflammatory low back pain in 2 out of 48 cases (4%) (Fig. 3).

## DISCUSSION

This study highlights the limitations of DETAIL and IBIS-q in screening patients with early IBD-related arthritis, particularly those with a predominant enthesal involvement. To the best of our knowledge, this is the first study comparing the screening performance of two questionnaires among patients with IBD. Furthermore, this study has led to the identification of 10 cases of IBD-related arthritis (5.6%), finding consistent with previous published studies [24].

The IBIS-q demonstrated superior screening performance for IBD-related arthritis compared to DETAIL, with significantly higher sensitivity. However, both questionnaires performed less effectively than in other tested cohorts [14, 15]. This discrepancy may be attributed to the higher prevalence of enthesitis in newly diagnosed IBD-related arthritis among our cases. Enthesitis is a poorly investigated domain in both questionnaires, with only one question each focusing on heel pain (questions nos. 3 and 1 for DETAIL and IBIS-q, respectively). However, only half of patients with active enthesitis at the diagnosis of IBD-related arthritis displayed Achilles tendon involvement, indicating the need for a screening tool that comprehensively assesses the enthesal aspect. IBD-related arthritis is classified under spondylarthritis, where enthesitis is considered a key early lesion of the joint disease [25–27]. However, the high frequency (i.e., 80%) of patients with a purely enthesal phenotype at onset, in the absence of peripheral swelling (i.e., synovitis), is undoubtedly a finding that is not seen in other case series [28], and is probably an expression of the short disease duration reported by patients, about 4 months. This is in line with etiopathogenetic studies that identify enthesitis as the initial inflammatory site before extending to the synovial level [26]. However, the limitations must also be considered, given the small number of diagnoses of IBD-related arthritis and the absence of diagnostic criteria for IBD



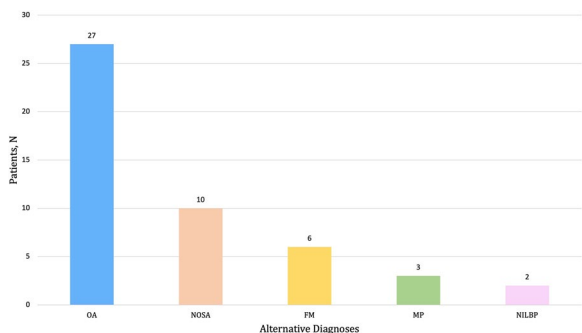
**Fig. 2** Sites of ultrasound confirmed enthesitis at the diagnosis of IBD-related arthritis

**Table 4** Performance of DETAIL and IBIS-q

	DETAIL	IBIS-q
True positive, <i>n</i> (%)	4/177 (2.3%)	7/177 (4.0%)
False positive, <i>n</i> (%)	26/177 (14.7%)	43/177 (24.3%)
False negative, <i>n</i> (%)	6/177 (3.4%)	3/177 (1.7%)
True negative, <i>n</i> (%)	141/177 (79.6%)	124/177 (70.0%)
Sensitivity	40.00% (95% CI 12.2–73.8)	70.00% (95% CI 34.8–93.3)
Specificity	84.43% (95% CI 78.0–89.6)	74.25% (95% CI 66.9–80.7)
Positive likelihood ratio	2.57 (95% CI 1.1–5.9)	2.72 (95% CI 1.68–4.4)
Negative likelihood ratio	0.71 (95% CI 0.4–1.2)	0.40 (95% CI 0.2–1.0)
Positive likelihood ratio	13.33% (95% CI 6.2–26.2)	14.00% (95% CI 9.1–20.9)
Negative likelihood ratio	95.92% (95% CI 93.4–97.5)	97.64% (95% CI 94.1–99)

*CI* confidence intervals





**Fig. 3** Alternative diagnosis in patients with at least one positive questionnaire. *OA* osteoarthritis, *NOSA* not otherwise specified arthralgia, *FM* fibromyalgia, *MP* myofascial pain, *NILBP* non-inflammatory low back pain

related arthritis and in general for peripheral SpA. Furthermore, how much the combination of clinical diagnosis associated with US evidence of enthesal inflammation could be the best diagnostic method needs to be verified in future studies [29].

Other limitations should be highlighted, mainly the monocentric nature of the study and a higher proportion of biological users compared to other cohorts, potentially influencing the clinical spectrum of SpA and its response to treatments targeting both gut and joints.

## CONCLUSIONS

This study highlights a significant proportion of new early diagnoses of arthritis among patients with IBD. In our cohort, the majority of newly identified cases of IBD-related arthritis displayed an enthesal involvement despite the absence of peripheral swelling. This finding delineates a patient phenotype that might pose challenges for gastroenterologists in recognition, and it likely represents an early stage before the disease spreads into synovial involvement [30]. Additionally, our results emphasize the importance of questions about enthesal domains to enhance the sensitivity of screening questionnaires, particularly for the detection of early forms of joint disease.

## ACKNOWLEDGEMENTS

We thank the participants of the study.

**Author Contributions.** Alen Zabotti: Investigation, conceptualization, writing, supervision, Review and Editing, Visualization; Nicola Cabas: Conceptualization, data curation, writing-original draft, Review and Editing, Formal analysis; Sofia Cacioppo: Investigation, Data curation, Writing – Review and Editing; Caterina Zoratti: Review and Editing, Formal analysis; Ivan Giovannini: Investigation, Writing – Review and Editing, Supervision; Debora Berretti: Investigation, Visualization; Michele Maria Luchetti: Supervision, Writing – Review and Editing; Salvatore De Vita and Giovanni Terrosu: Visualization, Supervision; Luca Quartuccio: Visualization, Supervision, Writing – Review and Editing; Marco Marino: Conceptualization, Review and Editing, Visualization.

**Funding.** No funding or sponsorship was received for this study or publication of this article.

**Data Availability.** Data generated and analyzed during the current study are available upon reasonable request to the corresponding author.

## Declarations

**Conflict of Interest.** Alen Zabotti is an Editorial Board member of *Rheumatology and Therapy*. Alen Zabotti was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Nicola Cabas, Sofia Cacioppo, Caterina Zoratti, Ivan Giovannini, Debora Berretti, Michele Maria Luchetti, Salvatore De Vita, Luca Quartuccio, Giovanni Terrosu, and Marco Marino declare no conflict of interest relevant for this study.

**Ethical Approval.** Informed consent was obtained from each patient in accordance with the Declaration of Helsinki and with local guidelines for good clinical practice. Ethical approvals

for the study were obtained (University of Udine, IRB 97/2023).

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