# Clinical phenotypes and therapeutic outcomes in enteropathic arthritis: a multivariate analysis from a retrospective cohort

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## Abstract

### Objective

*Enteropathic arthritis (SpA-IBD) refers to the coexistence of spondyloarthritis (SpA) and inflammatory bowel diseases (IBD). Whether the initial disease manifestation (SpA-first vs. IBD-first) influences clinical phenotypes and treatment outcomes remains uncertain. This study aimed to evaluate potential associations between disease onset and specific musculoskeletal manifestations, as well as to identify predictors of therapeutic multi-failure.*

### Methods

*We conducted a retrospective analysis of patients with SpA-IBD evaluated by both rheumatologists and gastroenterologists at our multidisciplinary ImmunoCenter from March 2022 to March 2024. We compared demographic, clinical, laboratory, and therapeutic characteristics of patients with SpA-first vs. IBD-first presentation. Multivariate logistic regression models were employed to assess associations between disease onset and clinical manifestations, and to identify predictors of therapeutic multi-failure.*

### Results

*Sixty-six patients were included (IBD-first: n=47, 71%; SpA-first: n=19, 29%). Enthesitis was more prevalent in the IBD-first group both at SpA onset (38% vs. 10%, p=0.021) and during follow-up (53% vs. 25%, p=0.034). No significant differences were observed in the frequency of axial (65% vs. 64%) and peripheral (60% vs. 66%) involvement or in laboratory parameters between the two groups. In the multivariate logistic regression, IBD-first presentation was significantly associated with a higher likelihood of developing enthesitis after adjusting for confounders (OR=0.267, 95% CI=0.076–0.942, p=0.040). Regarding treatment outcomes, psoriasis was significantly associated with increased risk of therapeutic multi-failure (OR=6.39, 95% CI=1.60–25.47, p=0.009), whereas other phenotypic features were not significantly predictive.*

### Conclusion

*The significantly higher likelihood of developing enthesitis in IBD-first suggests that distinct disease onset patterns and clinical phenotypes may influence musculoskeletal manifestations and treatment responses in enteropathic arthritis.*

**Key words**

spondyloarthritis, inflammatory bowel diseases, enteroarthritis, enthesitis, pathophysiology, gut-joint axis

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## Introduction

Patients with spondyloarthritis (SpA) may present with purely axial involvement or variable peripheral phenotypes, including arthritis, enthesitis, or dactylitis (1). SpA frequently coexists with other chronic inflammatory diseases, particularly inflammatory bowel disease (IBD), in 3-13% of cases (1, 2). Conversely, SpA is diagnosed in 6-64% of patients with Crohn's disease (CD) or ulcerative colitis (UC), with a higher prevalence in CD (3). The coexistence of these conditions, defined as enteropathic arthritis (SpA-IBD) (9), is supported by shared pathogenetic mechanisms (4-6) and therapeutic targets (6), the presence of subclinical joint and entheseal inflammation in 16-64% of IBD patients, and histological evidence of subclinical gut inflammation in up to 60% of SpA patients (7, 8).

Patients with SpA-IBD may experience different musculoskeletal phenotypes, which are not always synchronous with IBD activity (12, 13). The disease can manifest initially as either SpA (SpA-first) or IBD (IBD-first), with the latter being the most common presentation (10, 11). Despite growing evidence on the gut-joint axis and shared inflammatory pathways, limited data exist on how the order of disease onset influences musculoskeletal phenotypes and treatment outcomes. Given the complexity of managing SpA-IBD, a multidisciplinary approach involving gastroenterologists and rheumatologists is recommended, particularly for selecting therapies that are effective for both conditions (15).

In this study, we aimed to investigate two key aspects of SpA-IBD. First, we evaluated whether the order of disease onset (IBD-first *vs*. SpA-first) is associated with specific musculoskeletal manifestations, including axial involvement, peripheral arthritis, enthesitis, psoriasis, and uveitis. Second, we assessed the predictive value of clinical phenotypes in therapeutic multi-failure, defined as failure of at least two biologic or targeted synthetic DMARDs with different mechanisms of action.

## Materials and methods

### *Subjects*

We took advantage of the multidisciplinary SpA-IBD clinic within the Immuno-Center of the Humanitas Research Hospital and identified patients with coexisting diagnoses of SpA and IBD who were consecutively seen between March 2022 and March 2024. We included patients with SpA who fulfilled the ASAS classification criteria for axial or peripheral SpA (3), and patients with CD or UC according to ECCO criteria (4, 5). Of note, 27 (40%) patients with SpA also fulfilled the CASPAR classification criteria for psoriatic arthritis (6). The study was conducted according to the declaration of Helsinki; the local Ethics Committees approved the study protocol.

We collected demographic and clinical data at diagnosis and the last follow-up visit. Characteristics included the presence of the HLA-B27 allele (available in patients with the suspect of axial involvement), serum C reactive protein (CRP) and fecal calprotectin levels, the type of musculoskeletal involvement (isolated axial, isolated peripheral including arthritis, enthesitis, and dactylitis, or combined) and IBD patterns (CD, UC), and the location, extent, and behaviour of the disease, according to the Montreal classification criteria (7), past or current smoking habits, and other comorbidities or associated conditions. The musculoskeletal manifestations were clinically determined, including the presence of enthesitis, with the exception of the axial involvement for which MRI was used in the presence of inflammatory back pain. SpA-first was defined as the presence of inflammatory peripheral or axial joint involvement at disease presentation, without gastrointestinal signs or symptoms. Conversely, patients who presented with intestinal involvement and later developed clinical signs of peripheral or axial arthritis were classified as IBD-first. No patient had concomitant onset of SpA and IBD. SpA remission was based on the ASDAS score, with inactive disease as ASDAS <1.3 (8), while IBD remission required both clinical remission (absence of symptoms) and endoscopic remission based on the latest available colonoscopy report. The assessment of enthesitis was based on the clinical evaluation of the most frequent entheseal sites (*e.g.*

Achilles tendon, plantar fascia, costosternal junctions) performed by experienced rheumatologists during multidisciplinary evaluations. Imaging techniques, including ultrasound or MRI, were not performed in all patients. Axial involvement was suspected in the presence of inflammatory back pain and/or radiological signs of sacroiliitis or spinal involvement, based on x-ray or MRI, according to the ASAS classification criteria for axial SpA (3).

Treatment history was recorded at the last follow-up visit, and included non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional (cs), biological (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARD), together with mesalazine. Multi-drug failure was defined in patients who failed more than 2 b- or ts-DMARDs with different mechanisms of action.

*Statistical analysis*

The study protocol was designed prior to the data collection and analysis under the umbrella agreement that allows the collection of retrospective clinical data at our institution and approved by the local Humanitas IRB as protocol 60/24.

Descriptive statistics are presented as means with standard deviations (SD) or medians with interquartile ranges (IQRs) for continuous variables, and as absolute frequencies and percentages for categorical variables. All statistical analyses were conducted using STATA/IC 15.1 (revision 03 Feb 2020; StataCorp).

To investigate the association between disease onset (SpA-first *vs*. IBD-first) and specific clinical manifestations, we conducted a series of multivariable logistic regression models, where each main clinical feature (enthesitis, psoriasis, uveitis, axial involvement, peripheral involvement) was treated as a dependent variable, and disease onset was the primary predictor of interest. These models were adjusted for relevant confounders, including age, gender, and disease duration. The selection of confounders was based on a combination of prior literature review, statistical relevance, and expert consensus from a multidisciplinary team of physicians and methodologists.

For the second study objective, assessing predictors of therapeutic multi-failure, we performed a separate multivariable logistic regression analysis. In this model, multi-failure was the dependent variable, while independent variables included key clinical manifestations with age, sex, and disease duration as potential confounders.

The following clinical variables were included in the multivariable logistic regression models as covariates: age at SpA diagnosis, sex, and disease duration (calculated from the time of the first IBD or SpA diagnosis to the last available follow-up). In models assessing predictors of therapeutic multi-failure, the following disease features were also included: isolated axial involvement, isolated peripheral involvement, psoriasis, enthesitis, and uveitis. These were selected based on their potential influence on treatment outcomes, as suggested by previous literature and clinical experience.

Results from logistic regression models are presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding *p*-values. An OR >1.0 indicates an increased likelihood of the outcome in the exposure group compared to the reference category, while an OR <1.0 suggests a decreased probability.

Given the reported interdependence among specific musculoskeletal and extra-articular manifestations in enteropathic arthritis and spondyloarthritis (9-14) multiple testing correction using the False Discovery Rate (FDR) was not applied. Instead, statistical significance was interpreted within the context of previously established associations between disease features, as supported by the available literature. Missing data were not imputed, and analyses were conducted using complete cases. Model robustness was assessed through collinearity diagnostics, and in cases where high variance inflation factors (VIF >5) indicated potential multicollinearity, alternative model specifications were considered, such as variable exclusion or combination where clinically appropriate.

## Results

*General characteristics of the study population*

The demographic and clinical characteristics of patients with enteropathic arthritis (n=66) are illustrated in Table I. Among these, 47 patients (71%) had IBD-first onset (IBD-first), while 19 (29%) had SpA-first onset (IBD-first). At SpA onset, 41 patients (62%) presented with axial involvement, 43 (65%) with peripheral involvement, and only 19 (29%) with both phenotypes. Enthesitis was present at SpA onset in 20 patients (30%). Considering concomitant IBD, 39 patients (60%) had Crohn's disease (CD), and 28% had complications such as stenosis, abscesses, or fistulas. Most CD patients had ileal involvement (49%), while the predominant phenotype in UC was pancolitis (41%). Twenty-one /66 patients (33%) had HLA-B27 testing available and 43% tested positive. Ongoing treatments at the last follow-up included low-dose glucocorticoids (24%), all ≤5 mg prednisone equivalent, NSAIDs (30%), and conventional DMARDs (methotrexate in 18%, sulfasalazine in 12%). Biologic therapies were used in 42% of patients, predominantly TNF inhibitors (adalimumab, infliximab, golimumab, certolizumab), while 23% were receiving ustekinumab, 22% vedolizumab, and 10% JAK inhibitors (upadacitinib or tofacitinib). At the last follow-up, 54% of IBD patients were in clinical and endoscopic remission, while SpA remission was observed in 56% of cases. However, concomitant remission of both diseases was achieved in only 29% of patients. Multi-drug failure was observed in 38% of cases.

*Comparison of clinical characteristics based on disease onset*

The demographic and clinical characteristics of SpA-first and IBD-first patients are summarised in Table II. Among musculoskeletal manifestations, enthesitis was significantly more frequent in the IBD-first group, both at SpA onset (38% *vs*. 10% in SpA-first, $p$=0.021) and during follow-up (53% *vs*. 25% in SpA-first, $p$=0.034). No significant differences were observed between IBD-first and SpA-first patients regarding ax-

**Table I.** Baseline demographic and clinical characteristics of the study population.

| | n=66 |
|---|---|
| Age at inclusion, years, mean (SD) | 49 (12) |
| Male gender, n. (%) | 29 (44) |
| Disease duration, years, mean (SD) | 14 (10) |
| Positive familiar history, n. (%) | 19 (29) |
| BMI, mean (SD) | 24 (4) |
| Smoke ever, n. (%) | 41 (62) |
| Dyslipidaemia, n. (%) | 7 (11) |
| Hypertension, n. (%) | 15 (23) |
| Cancer, n. (%) | 13 (20) |
| Depression, n. (%) | 6 (9) |
| CAD, n. (%) | 4 (6) |
| Diabetes mellitus, n. (%) | 4 (6) |
| Fibromyalgia, n. (%) | 9 (14) |
| SpA-first onset, n. (%) | 19 (29) |
| Axial involvement at onset, n. (%) | 41 (62) |
| Peripheral involvement at onset, n. (%) | 43 (65) |
| Peripheral + axial at onset, n. (%) | 19 (29) |
| Enthesitis at onset, n. (%) | 20 (30) |
| Axial involvement only, n. (%) | 16 (24) |
| Peripheral involvement only, n. (%) | 21 (32) |
| Peripheral + axial involvement, n. (%) | 29 (44) |
| Enthesitis ever, n. (%) | 30 (45) |
| Dactylitis ever, n. (%) | 4 (6) |
| Psoriasis ever, n. (%) | 25 (38) |
| Nail psoriasis ever, n. (%) | 7 (11) |
| Uveitis ever, n. (%) | 6 (9) |
| Erythema nodosum ever, n. (%) | 4 (6) |
| CASPAR fulfilment, n. (%) | 27 (41) |
| Crohn's disease, n. (%) | 39 (60) |
| Crohn' disease - localisation: | |
| Ileal, n. (%) | 19 (49) |
| Colic, n. (%) | 15 (38) |
| Ileo-colic, n. (%) | 4 (15) |
| All digestive, n. (%) | 2 (5) |
| Crohn's disease - phenotype: | |
| Inflammatory n. (%) | 22 (56) |
| Stenosing n. (%) | 17 (44) |
| Fistulous, n. (%) | 5 (13) |
| With perianal involvement, n. (%) | 7 (18) |
| Ulcerative colitis - extent: | |
| Rectum, n. (%) | 5 (18) |
| Colon, n. (%) | 9 (33) |
| Pancolitis, n. (%) | 11 (41) |
| Other, n. (%) | 2 (8) |
| IBD complications, n. (%) | 28 (42) |
| SpA remission, n. (%) | 37 (56) |
| IBD remission, n. (%) | 36 (54) |
| Both SpA and IBD remission, n. (%) | 19 (28) |
| HLA-B27, n. (%) | 3/21 (18) |
| CRP at onset md/dL, mean (SD) | 0.4 (0.5) |
| CRP mg/dL, mean (SD) | 1 (1) |
| Calprotectin at onset, ug/g, mean (SD) | 678 (1049) |
| Calprotectin, ug/g, mean (SD) | 132 (211) |

BMI: Body Mass index; CAD: cardiovascular disease; SpA: spondylarthritis; CASPAR: ClASsification criteria for Psoriatic Arthritis; IBD: inflammatory bowel disease; HLA-B27: human leukocyte antigen-B27; CRP: C-reactive protein.

**Table II.** Demographic and clinical characteristic of the study population, stratified by type of onset.

| | SpA-first n=19 | IBD-first n=47 |
|---|---|---|
| Age at inclusion, years, mean (SD) | 51 (12) | 49 (12) |
| Male gender, n. (%) | 11 (58) | 18 (38) |
| Disease duration, years, mean (SD) | 11 (10) | 15 (10) |
| Positive familiar history, n. (%) | 7 (37) | 12 (25) |
| **BMI, mean (SD)** | **25 (5)** | **23 (4)** |
| Smoke ever, n. (%) | 13 (68) | 28 (60) |
| Dyslipidaemia, n. (%) | 3 (16) | 4 (8) |
| Hypertension, n. (%) | 5 (26) | 10 (21) |
| Cancer ever, n. (%) | 4 (21) | 9 (19) |
| Depression, n. (%) | 3 (16) | 3 (6) |
| CAD, n. (%) | 2 (10) | 2 (4) |
| Diabetes mellitus, n. (%) | 2 (10) | 2 (4) |
| Fibromyalgia, n. (%) | 3 (16) | 6 (13) |
| Axial involvement at onset, n. (%) | 12 (63) | 29 (62) |
| Peripheral involvement at onset, n. (%) | 12 (63) | 31 (66) |
| Peripheral + axial at onset, n. (%) | 5 (26) | 14 (30) |
| **Enthesitis at onset, n. (%)** | **2 (10)** | **18 (38)** |
| Axial involvement only, n. (%) | 4 (21) | 12 (25) |
| Peripheral involvement only, n. (%) | 8 (42) | 13 (28) |
| Peripheral + axial involvement, n. (%) | 7 (37) | 22 (47) |
| **Enthesitis ever, n. (%)** | **5 (26)** | **25 (53)** |
| Dactylitis ever, n. (%) | 0 | 4 (8) |
| Psoriasis ever, n. (%) | 7 (37) | 18 (38) |
| Nail psoriasis ever, n. (%) | 0 | 7 (15) |
| Uveitis ever, n. (%) | 2 (10) | 4 (8) |
| Erythema nodosum ever, n. (%) | 3 (6) | 1 (1) |
| CASPAR fulfilment, n. (%) | 5 (26) | 22 (47) |
| Crohn's disease, n. (%) | 13 (69) | 26 (55) |
| **IBD disease duration, years, mean (SD)** | **4 (4)** | **15 (10)** |
| IBD complications, n. (%) | 8 (40) | 23 (49) |
| SpA remission, n. (%) | 8 (40) | 29 (62) |
| IBD remission, n. (%) | 10 (53) | 26 (55) |
| Both SpA and IBD remission, n. (%) | 4 (20) | 15 (32) |
| HLA-B27, n. (%) | 2/5 (48) | 1/16 (6.3) |
| **CRP at onset md/dL, mean (SD)** | **7 (8)** | **2 (4)** |
| **CRP mg/dL, mean (SD)** | **1 (2)** | **0.5 (0.6)** |
| Calprotectin at onset, ug/g, mean (SD) | 661 (1188) | 594 (859) |
| Calprotectin, ug/g, mean (SD) | 104 (125) | 143 (238) |
| Current glucocorticoids, n. (%) | 6 (31) | 10 (21) |
| Current NSAIDs, n. (%) | 6 (32) | 13 (28) |
| Current salazopyrin, n. (%) | 1 (5) | 7 (15) |
| Current mesalazine, n. (%) | 2 (10) | 10 (21) |
| Current MTX, n. (%) | 5 (26) | 7 (15) |
| Current anti-TNF, n. (%) | 7 (37) | 21 (45) |
| Current ustekinumab, n. (%) | 5 (26) | 10 (21) |
| Current vedolizumab, n. (%) | 2 (10) | 12 (27) |
| Current tsDMARDs, n. (%) | 1 (5) | 6 (13) |
| upadacitinib, n. | 1 | 4 |
| tofacitinib, n. | 0 | 2 |
| Drug multi-failure, n. (%) | 7 (39) | 18 (40) |

BMI: Body Mass index; CAD: cardiovascular disease; SpA: spondylarthritis; CASPAR: ClASsification criteria for Psoriatic Arthritis; IBD: inflammatory bowel disease; HLA-B27: human leukocyte antigen-B27; CRP: C-reactive protein; NSAIDs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; TNF: tumour necrosis factor; IL12/23: interleukin 12/23; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs.

ial (65% *vs*. 64%) and peripheral (60% *vs*. 66%) involvement, age of onset, laboratory features, or ongoing treatments. Serum CRP levels were higher in the SpA-first group, both at disease onset (7±8 *vs*. 2±4 mg/dL in IBD-first, $p$=0.009) and at last follow-up (1±2 *vs*. 0.5±0.6 mg/dL in IBD-first, $p$=0.012). HLA-B27 was more frequent in the SpA-first group (50% *vs*. 6%), though this difference did not reach statistical significance ($p$=0.060). Fecal calprotectin and other laboratory parameters showed no significant differences.

### *Association between disease onset and clinical manifestations*

Through multivariate logistic regression analysis adjusted for age, sex, and

**Table III.** Demographic and clinical characteristic of the study population, stratified by rheumatological phenotype.

| | Axial only n=16 | | Peripheral only n=21 | | Peripheral + axial n=29 | |
|---|---|---|---|---|---|---|
| Age at inclusion, years, mean (SD) | 51 (11) | 0.639 | 50 (12) | 0.635 | 48 (12) | 0.909 |
| Male sex, n. (%) | 5 (31) | 0.240 | 7 (33) | 0.236 | **17 (59)** | **0.033** |
| Disease duration, years, mean (SD) | 10 (7) | 0.071 | 15 (12) | 0.186 | 15 (11) | 0.928 |
| Positive familiar history, n. (%) | 3 (19) | 0.308 | 7 (33) | 0.577 | 9 (31) | 0.721 |
| BMI, mean (SD) | 24 (4) | 0.806 | 24 (5) | 0.472 | 23 (4) | 0.364 |
| Smoke ever, n. (%) | 11 (69) | 0.530 | **9 (43)** | **0.028** | 21 (72) | 0.127 |
| Dyslipidaemia, n. (%) | 3 (19) | 0.224 | 2 (9) | 0.845 | 2 (7) | 0.386 |
| Hypertension, n. (%) | 6 (37) | 0.105 | 6 (29) | 0.439 | **3 (10)** | **0.034** |
| Cancer ever, n. (%) | 4 (25) | 0.540 | 4 (19) | 0.928 | 5 (17) | 0.657 |
| Depression, n. (%) | 0 | 0.146 | 3 (14) | 0.316 | 3 (10) | 0.754 |
| CAD, n. (%) | 1 (6) | 0.971 | 2 (9) | 0.421 | 1 (3) | 0.431 |
| Diabetes mellitus, n. (%) | 1 (6) | 0.971 | 2 (9) | 0.421 | 1 (3) | 0.431 |
| Fibromyalgia, n. (%) | 1 (6) | 0.323 | 5 (24) | 0.100 | 3 (10) | 0.490 |
| Primarily-SpA onset n. (%) | 4 (25) | 0.701 | 8 (38) | 0.254 | 7 (24) | 0.460 |
| Enthesitis ever, n. (%) | 4 (25) | 0.059 | 12 (57) | 0.193 | 14 (48) | 0.684 |
| Dactylitis ever, n. (%) | 0 | 0.243 | 2 (9) | 0.421 | 2 (7) | 0.801 |
| Psoriasis ever, n. (%) | 6 (37) | 0.971 | 5 (24) | 0.107 | 14 (48) | 0.123 |
| Nail psoriasis ever, n. (%) | 2 (12) | 0.777 | 1 (5) | 0.292 | 4 (14) | 0.457 |
| Uveitis ever, n. (%) | 1 (6) | 0.650 | 2 (9) | 0.933 | 3 (10) | 0.754 |
| Erythema nodosum ever, n. (%) | 2 (12) | 0.215 | 1 (5) | 0.763 | 1 (3) | 0.431 |
| Crohn's disease, n. (%) | 10 (62) | 0.750 | 10 (48) | 0.195 | 19 (65) | 0.347 |
| IBD complication, n. (%) | 9 (56) | 0.199 | 7 (33) | 0.307 | 12 (41) | 0.879 |
| SpA remission, n. (%) | 11 (69) | 0.240 | 11 (52) | 0.681 | 15 (52) | 0.530 |
| IBD remission, n. (%) | **5 (31)** | **0.032** | 14 (67) | 0.177 | 17 (59) | 0.556 |
| Both SpA and IBD remission, n. (%) | 4 (25) | 0.733 | 6 (29) | 0.979 | 9 (30) | 0.788 |
| HLA-B27, n. (%) | 0/3 (0) | 0.445 | 0/4 (0) | 0.364 | 3/14 (27) | 0.186 |
| CRP at onset md/dL, mean (SD) | 2 (3) | 0.056 | 4 (8) | 0.153 | 4 (5) | 0.756 |
| CRP mg/dL, mean (SD) | 0.80 (1) | 0.433 | 0.81 (1.5) | 0.204 | 0.54 (0.74) | 0.068 |
| Calprotectin at onset, ug/g, mean (SD) | 301 (242) | 0.066 | 808 (1454) | 0.391 | 789 (1010) | 0.443 |
| Calprotectin, ug/g, mean (SD) | 150 (250) | 0.675 | 129 (244) | 0.791 | 123 (166) | 0.546 |
| Current glucocorticoids, n. (%) | 2 (12) | 0.195 | 6 (29) | 0.609 | 8 (29) | 0.520 |
| Current NSAIDs, n. (%) | 2 (12) | 0.090 | 9 (43) | 0.095 | 8 (29) | 0.919 |
| Current salazopyrin, n. (%) | 3 (19) | 0.351 | 2 (9) | 0.659 | 3 (10) | 0.695 |
| Current mesalazine, n. (%) | 3 (19) | 0.920 | 5 (24) | 0.418 | 4 (14) | 0.413 |
| Current MTX, n. (%) | 3 (19) | 0.946 | 4 (19) | 0.901 | 5 (17) | 0.861 |
| Current anti-TNF, n. (%) | 7 (44) | 0.902 | 9 (43) | 0.961 | 12 (41) | 0.879 |
| Current ustekinumab, n. (%) | 3 (19) | 0.663 | 4 (19) | 0.626 | 8 (28) | 0.404 |
| Current vedolizumab, n. (%) | 4 (27) | 0.608 | 4 (19) | 0.702 | 6 (21) | 0.939 |
| Current tsDMARDs, n. (%) | 0 | 0.113 | 2 (9) | 0.845 | 5 (17) | 0.121 |
| Drug multi-failure, n. (%) | 5 (33) | 0.565 | 6 (32) | 0.388 | 14 (48) | 0.198 |

BMI: Body Mass index; CAD: cardiovascular disease; SpA: spondylarthritis; CASPAR: ClASsification criteria for Psoriatic Arthritis; IBD: inflammatory bowel disease; HLA-B27: human leukocyte antigen-B27; CRP: C-reactive protein; NSAIDs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; TNF: tumour necrosis factor; IL12/23: interleukin 12/23; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs.

disease duration, we found that patients with IBD-first onset had a significantly higher likelihood of developing enthesitis compared to those with SpA-first onset (OR=0.27, 95% CI=0.08–0.94, $p$=0.040) (Table III). However, no significant associations were observed between disease onset and other musculoskeletal features, including axial involvement, peripheral arthritis, dactylitis, psoriasis, and uveitis.

*Predictors of therapeutic multi-failure*

To explore potential predictors of treatment resistance, we conducted a multivariate logistic regression analysis using therapeutic multi-failure as the dependent variable. Psoriasis emerged as a significant predictor of therapeutic failure, with an odds ratio of 6.39 (95% CI=1.60–25.47, $p$=0.009), indicating that patients with psoriasis had a markedly increased likelihood of failing multiple biologic or targeted synthetic DMARDs. Enthesitis and other musculoskeletal manifestations were not significantly associated with therapeutic failure. Disease duration was also independently associated with a multi-failure status (OR=1.09, 95% CI=1.01–1.18, $p$=0.021).

## Discussion

Enteropathic arthritis is the least studied subset of the SpA spectrum disorders despite the rapidly evolving evidence on IBD and SpA as separate entities, and the clinical, pathophysiological, and treatment aspects have a wide heterogeneity often requiring a multidisciplinary approach. Specific musculoskeletal and extra-articular manifestations of IBD-related arthritis have been shown to be closely associated, highlighting the strong interconnection between intestinal inflammation and joint involvement (gut-joint axis). This relationship has been extensively discussed and demonstrated, reinforcing the concept of an interdependence among specific musculoskeletal and extra-articular manifestations which cannot be considered as fully independent (9-14).

Our data are based on a multidisciplinary approach and provide novel evidence that enthesitis may more commonly represent the initial manifestation in patients where IBD precedes SpA. Additionally, our findings highlight the challenge of achieving simultaneous remission of both conditions, with only 29% of patients reaching this outcome.

Our cohort of 66 patients with IBD-associated SpA allowed to focus on the clinical and laboratory characteristics, evaluating potential differences between patients presenting first with rheumatological manifestations (SpA-first) and those developing IBD first (IBD-first). In the majority of patients (71%) gastro-intestinal manifestations preceded joint disease and in particular CD was the most common IBD associated with SpA manifestations, in line with previous data (15, 16). The higher frequency of the IBD-first phenotype in our cohort supports the consolidated hypothesis considering gut inflammation as a key player in the pathogenesis of SpA (17, 18). In fact, in last decades several authors investigated and revisited the gut-joint and most of all the gut-enthesis axis demonstrating that, in genetic predisposed animals prone to develop SpA, similar to the SKG mu-

**Table IV.** Multivariate logistic regression models were performed to assess the association between disease onset type and specific musculoskeletal manifestations.

| | Odds ratio | Std. err. | P>\|z\| | [95% Conf. interval] |
|---|---|---|---|---|
| Peripheral involvement | 2.59939 | 1.610268 | 0.123 | 0.7719156–8.753327 |
| Axial involvement | 0.4793469 | 0.3540511 | 0.319 | 0.1127049–2.038718 |
| Psoriasis | 0.5885032 | 0.3609912 | 0.387 | 0.1768548–1.958307 |
| Enthesitis | 0.2672108 | 0.1717069 | 0.040 | 0.0758369–0.9415153 |
| Uveitis | 0.8815217 | 0.8916577 | 0.901 | 0.1214071–6.400618 |

The outcomes are listed in the first column, representing different clinical features. Odds ratios (ORs) refer to the likelihood of presenting each musculoskeletal feature in patients with SpA-first onset (reference category: IBD-first onset). An OR >1 indicates a higher probability of having the respective manifestation in SpA-first onset patients, whereas an OR <1 suggests a lower probability compared to IBD-first onset patients. The models were adjusted for potential confounders, including age, sex, and disease duration. 95% confidence intervals (CIs) and *p*-values are provided for statistical interpretation.

**Table V.** Therapeutic multi-failure: univariate and multivariate logistic regression.

| Variabile | OR Univariate | IC 95% Univariate | *p* Univariate | OR Multivariate | IC 95% Multivariate | *p* Multivariate |
|---|---|---|---|---|---|---|
| Peripheral involvement | 2.599 | (0.77–8.75) | 0.123 | 0.805 | (0.17–3.85) | 0.786 |
| Axial involvement | 0.479 | (0.11–2.04) | 0.319 | 1.237 | (0.20–7.64) | 0.818 |
| Psoriasis | 0.588 | (0.18–1.96) | 0.387 | 6.389 | (1.60–25.47) | 0.009 |
| Enthesitis | 0.267 | (0.08–0.94) | 0.040 | 0.838 | (0.21–3.42) | 0.806 |
| Uveitis | 0.881 | (0.12–6.40) | 0.901 | 1.000 | Omitted | - |

This table presents odds ratios (OR) with corresponding 95% confidence intervals (CI) and *p*-values for both univariate and multivariate analyses. The outcome analysed is therapeutic multi-failure, while the predictive variables are listed in the first column. The univariate columns show the results of univariate logistic regression for each predictor variable. The multivariate columns show the results of the multivariate logistic regression model, adjusting for potential confounders. OR >1 indicates an increased probability of the outcome (multi-failure), whereas OR <1 indicates a reduced probability. Omitted values indicate variables excluded from the model due to collinearity or lack of significance.

rine model, intestinal inflammation is a trigger for entheseal inflammation (19, 20). The mouse experimental models suggest that a disruption in the gut barrier results in a dysfunctional interaction between the mucosal immune system and the gut microbiota representing the *primum movens* in SpA (21). This in turn perpetuates a gut-joint axis involving trafficking of cells between the gut and the joint or enthesis (22), including mucosa-associated T invariant (MAIT) cells (23) and microbial translocation (24-26). Hence, *in vitro* evidence of immune cell homing from the intestinal mucosa to the entheses (27) may in part explain the intimate connection between the gut and the entheses and why the entheses are the epicenter of inflammation in the patient with both SpA and IBD.

We are intrigued by the observation that our results are consistent with the working hypothesis as enthesitis is the earliest feature of SpA in patients already diagnosed with IBD. Furthermore, enthesitis is the most common musculoskeletal manifestation observed in the IBD-first group throughout the disease course, while other disease domains are equally distributed in the cohort. This finding, if confirmed, may have potential implications in clinical practice and influence the decisional algorithms for the management of this complex disease. According to the current guidelines (28, 29), the goal of IBD treatment is to inhibit intestinal inflammation and reduce the risk of complications, but some of drugs recommended as first-line therapy (*i.e.* mesalazine or topical drugs) have no efficacy on this musculoskeletal domain. Conversely, drugs used as first line treatment for arthritis, such as sulfasalazine or MTX, also have some efficacy on the intestinal inflammation. This might further explain why in most patients gut disease predates joint manifestations, as also observed in our study. However, as demonstrated in other autoimmune diseases (30), immunomodulatory treatment is apparently unable to reverse the pathogenetic mechanisms underlying disease development, and this explains the occurrence of joint disease during IBD irrespective of treatments.

The prevalence of different musculoskeletal phenotypes of SpA-IBD remains poorly defined, leading to substantial variation in case-finding methods across studies (31–33) and reducing the reliability of phenotype comparisons in the literature. In our cohort, the HLA-B27 allele was more frequent in SpA-first patients compared to the IBD-first onset. Regarding SpA phenotypes, musculoskeletal involvement showed a balanced distribution, with 62% of patients presenting axial involvement, 65% peripheral involvement, and 29% exhibiting both, aligning with existing literature (34). Moreover, in patients with combined phenotype (peripheral plus axial manifestations) we reported a higher prevalence of male sex and HLA-B27 allele compared to those with isolated axial or peripheral involvement.

Furthermore, significantly higher CRP levels are observed in the SpA-first group suggesting more inflammatory phenotype both at disease onset as at last visit, while fecal calprotectin levels and other laboratory markers did not differ significantly. Previous studies and meta-analyses reported an increased risk of psoriasis and PsA in the IBD population, especially for CD (35-37). Since the immune mechanisms of IBD and SpA are largely shared also by psoriasis, the clinical characteristics of this subgroup of patients with both SpA-IBD and psoriasis may hold pathogenetic significance. As many as 40% of our patients with SpA-IBD also fulfilled the CASPAR classification criteria for PsA (with a family or personal history of skin and/or nail psoriasis) and these presented more frequently as IBD-first, thus reinforcing the hypothesis of an intestinal primary mechanism in the pathogenesis of SpA and related disorders, including PsA. This subgroup of patients also has a higher risk of failing multiple lines of therapy, likely due to a longer disease duration. Of note, patients with SpA-IBD and psoriasis displayed a more frequent use of ustekinumab at gastrointestinal dosage. Despite the efforts of a multidiscipli-

nary gastro-rheumatological approach, less than 30% of SpA-IBD patients are in remission at the last available time-point, suggesting divergent trajectories of the two diseases. In our cohort, no musculoskeletal manifestations were significantly associated with treatment resistance, whereas concomitant psoriasis was significantly more likely to result in failure of multiple biologic or targeted synthetic DMARDs. We hypothesise that this may be due to the suboptimal response of psoriatic skin disease to TNF inhibitors, which are more commonly used as first-line therapies in IBD, as well as the increased inflammatory burden of psoriasis (38), which further complicates achieving adequate disease control. Lastly, we identified disease duration as an additional independent predictor of multi-failure status in our population, emphasising the need for early and aggressive intervention.

We are aware of the limitations of our study, primarily related to the retrospective design and the impossibility to discern the influence of treatments on the incidence of the clinical manifestations over time. However, we did not observe an increased risk of SpA development related to IL17 inhibitors as none of the patients in the IBD-first group has previously treated with this class of bDMARDs. Further, HLA B27 typing is missing in the majority of patients, and this limits our analysis of their potential correlations with disease phenotypes. While we cannot determine the reasons for the missing data in all cases, we should note that this genetic test is prescribed at our Institution only in the suspicion of an axial inflammatory involvement.

In conclusion, we confirm the substantial clinical heterogeneity of patients with IBD and SpA and report for the first time that enthesitis is more frequently the initial manifestation in patients with IBD who will develop SpA, suggesting new hints for an early diagnosis. We also demonstrate that the control of both IBD and SpA remains a major therapeutic challenge, despite a multidisciplinary management. Axial involvement is associated with a reduced chance of achieving IBD remission, while concomitant psoriasis and prolonged disease duration are key factors associated with a higher likelihood of treatment failure. While prospective studies are awaited, our data suggest the existence of a pathogenetic cascade that, over time, may lead to the different phenotypes observed in patients with enteropathic arthritis.

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## References

1. FATTORINI F, GENTILESCHI S, CIGOLINI C *et al*.: Axial spondyloarthritis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(11): 2142-50. https://doi.org/10.55563/clinexprheumatol/9fhz98
2. FARISOĞULLARI B, YARDIMCI GK, SARI A *et al*.: Is the impact of biologic agents in enteropathic spondylitis different from other spondylitis? Real life data from the HUR-BIO Registry. *Clin Exp Rheumatol* 2022; 40(1): 112-19. https://doi.org/10.55563/clinexprheumatol/uxcofr
3. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011; 70(1): 25-31. https://doi.org/10.1136/ard.2010.133645
4. GOMOLLÓN F, DIGNASS A, ANNESE V *et al*.: 3rd European Evidence-based Consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis* 2017; 11(1): 3-25. https://doi.org/10.1093/ecco-jcc/jjw168
5. MAGRO F, GIONCHETTI P, ELIAKIM R *et al*.: Third European Evidence-based Consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017; 11(6): 649-70. https://doi.org/10.1093/ecco-jcc/jjx008
6. TAYLOR W, GLADMAN D, HELLIWELL P *et al*.: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54(8): 2665-73. https://doi.org/10.1002/art.21972
7. SILVERBERG MS, SATSANGI J, AHMAD T *et al*.: Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; 19 Suppl A: 5A-36A. https://doi.org/10.1155/2005/269076
8. MACHADO P, LANDEWÉ R, LIE E *et al*.: Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70(1): 47-53. https://doi.org/10.1136/ard.2010.138594
9. LÓPEZ-MEDINA C, ORTEGA-CASTRO R, CASTRO-VILLEGAS MC *et al*.: Axial and peripheral spondyloarthritis: does psoriasis influence the clinical expression and disease burden? Data from REGISPONSER registry. *Rheumatology* (Oxford) 2021; 60(3): 1125-36. https://doi.org/10.1093/rheumatology/keaa398
10. KHROM M, LONG M, DUBE S *et al*.: Comprehensive association analyses of extraintestinal manifestations in inflammatory bowel disease. *Gastroenterology* 2024; 167(2): 315-32. https://doi.org/10.1053/j.gastro.2024.02.026
11. CANTINI F, NICCOLI L, NANNINI C *et al*.: Case-control study on dactylitis, enthesitis, and anterior uveitis in spondyloarthritis associated with inflammatory bowel diseases: role of coexistent psoriasis. *J Rheumatol* 2017; 44(9): 1341-46. https://doi.org/10.3899/jrheum.161518
12. MEASE PJ, LIU M, REBELLO S *et al*.: Disease characteristics, quality of life, and work productivity by enthesitis site: real-world data from the US Corrona Psoriatic Arthritis/Spondyloarthritis Registry. *J Rheumatol* 2021; 48(3): 367-75. https://doi.org/10.3899/jrheum.191117
13. ALIZADEH M, WONG U, SIATON BC *et al*.: Inflammatory bowel disease-associated arthritis is associated with concomitant autoimmune and inflammatory disorders. *Dig Dis Sci* 2024; 69(8): 2961-69. https://doi.org/10.1007/s10620-024-08478-7
14. MICHELENA X, SEPRIANO A, ZHAO SS *et al*.: Exploring the unifying concept of spondyloarthritis: a latent class analysis of the REGISPONSER registry. *Rheumatology* (Oxford) 2024; 63(11): 3098-105. https://doi.org/10.1093/rheumatology/keae005
15. SALVARANI C, FRIES W: Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease. *World J Gastroenterol* 2009; 15(20): 2449. https://doi.org/10.3748/wjg.15.2449
16. OLIVIERI I, CANTINI F, CASTIGLIONE F *et al*.: Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease. *Autoimmun Rev* 2014; 13(8): 822-30. https://doi.org/10.1016/j.autrev.2014.04.003
17. GRACEY E, VEREECKE L, MCGOVERN D *et al*.: Revisiting the gut-joint axis: links between gut inflammation and spondyloarthritis. *Nat Rev Rheumatol* 2020; 16(8): 415-33. https://doi.org/10.1038/s41584-020-0454-9
18. MAURO D, NAKAMURA A, HAROON N, CICCIA F: The gut-enthesis axis and the pathogenesis of spondyloarthritis. *Semin Immunol* 2021; 58: 101607. https://doi.org/10.1016/j.smim.2022.101607
19. BENHAM H, REHAUME LM, HASNAIN SZ *et al*.: Interleukin-23 mediates the intestinal response to microbial β-1,3-glucan and the development of spondyloarthritis pathology in SKG mice. *Arthritis Rheumatol* 2014; 66(7): 1755-67. https://doi.org/10.1002/art.38638
20. WATAD A, CUTHBERT RJ, AMITAL H, MCGONAGLE D: Enthesitis: much more than focal insertion point inflammation. *Curr Rheumatol Rep* 2018; 20(7): 41.

https://doi.org/10.1007/s11926-018-0751-3
21. GIONCHETTI P, CALABRESE C, RIZZELLO F: Inflammatory bowel diseases and spondyloarthropathies. *J Rheumatol Suppl* 2015; 93: 21-23. https://doi.org/10.3899/jrheum.150628
22. LI Y, DU J, WEI W: Emerging roles of mucosal-associated invariant T cells in rheumatology. *Front Immunol* 2022; 13: 819992. https://doi.org/10.3389/fimmu.2022.819992
23. RAYCHAUDHURI SK, ABRIA C, MITRA A, RAYCHAUDHURI SP: Functional significance of MAIT cells in psoriatic arthritis. *Cytokine* 2020; 125: 154855. https://doi.org/10.1016/j.cyto.2019.154855
24. YU DTY: Molecular mimicry in HLA-B27-related arthritis. *Ann Intern Med* 1989; 111(7): 581. https://doi.org/10.7326/0003-4819-111-7-581
25. CLEGG DO, ZONE JJ, SAMUELSON CO, WARD JR: Circulating immune complexes containing secretory IgA in jejunoileal bypass disease. *Ann Rheum Dis* 1985; 44(4): 239-44. https://doi.org/10.1136/ard.44.4.239
26. BERTHELOT J-M, WENDLING D: Translocation of dead or alive bacteria from mucosa to joints and epiphyseal bone-marrow: facts and hypotheses. *Joint Bone Spine* 2020; 87(1): 31-36. https://doi.org/10.1016/j.jbspin.2019.01.004
27. SHARIF K, BRIDGEWOOD C, DUBASH S, MCGONAGLE D: Intestinal and enthesis innate immunity in early axial spondyloarthropathy. *Rheumatology* (Oxford) 2020; 59(Supplement_4): iv67-78. https://doi.org/10.1093/rheumatology/keaa408
28. LICHTENSTEIN GR, LOFTUS EV, ISAACS KL, REGUEIRO MD, GERSON LB, SANDS BE: ACG Clinical Guideline: Management of Crohn's disease in adults. *Am J Gastroenterol* 2018; 113(4): 481-517. https://doi.org/10.1038/ajg.2018.27
29. RUBIN DT, ANANTHAKRISHNAN AN, SIEGEL CA, SAUER BG, LONG MD: ACG Clinical Guideline: Ulcerative colitis in adults. *Am J Gastroenterol* 2019; 114(3): 384-413. https://doi.org/10.14309/ajg.0000000000000152
30. KRIJBOLDER DI, VERSTAPPEN M, VAN DIJK BT *et al*.: Intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden (TREAT EARLIER): a randomised, double-blind, placebo-controlled, proof-of-concept trial. *Lancet* 2022; 400(10348): 283-94. https://doi.org/10.1016/S0140-6736(22)01193-x
31. MALATY HM, LO GH-W, HOU JK: Characterization and prevalence of spondyloarthritis and peripheral arthritis among patients with inflammatory bowel disease. *Clin Exp Gastroenterol* 2017; 10: 259-63. https://doi.org/10.2147/ceg.s136383
32. OSSUM AM, PALM Ø, LUNDER AK *et al*.: Ankylosing spondylitis and axial spondyloarthritis in patients with long-term inflammatory bowel disease: results from 20 years of follow-up in the IBSEN Study. *J Crohns Colitis* 2018; 12(1): 96-104. https://doi.org/10.1093/ecco-jcc/jjx126
33. LUCHETTI MM, BENFAREMO D, BENDIA E *et al*.: Clinical and patient reported outcomes of the multidisciplinary management in patients with inflammatory bowel disease-associated spondyloarthritis. *Eur J Intern Med* 2019; 64: 76-84. https://doi.org/10.1016/j.ejim.2019.04.015
34. SHIVASHANKAR R, LOFTUS E V, TREMAINE WJ *et al*.: Incidence of spondyloarthropathy in patients with Crohn's disease: a population-based study. *J Rheumatol* 2012; 39(11): 2148-52. https://doi.org/10.3899/jrheum.120321
35. EGEBERG A, MALLBRIS L, WARREN RB *et al*.: Association between psoriasis and inflammatory bowel disease: a Danish nationwide cohort study. *Br J Dermatol* 2016; 175(3): 487-92. https://doi.org/10.1111/bjd.14528
36. MOON JM, LEE JY, KOH S-J *et al*.: Incidence of psoriasis in patients with inflammatory bowel disease: a nationwide population-based matched cohort study. *Dermatology* 2021; 237(3): 330-37. https://doi.org/10.1159/000514030
37. ALINAGHI F, TEKIN HG, BURISCH J, WU JJ, THYSSEN JP, EGEBERG A: Global prevalence and bidirectional association between psoriasis and inflammatory bowel disease – a systematic review and meta-analysis. *J Crohns Colitis* 2020; 14(3): 351-60. https://doi.org/10.1093/ecco-jcc/jjz152
38. MAN A-M, ORĂSAN MS, HOTEIUC O-A, OLĂNESCU-VAIDA-VOEVOD M-C, MOCAN T: Inflammation and psoriasis: a comprehensive review. *Int J Mol Sci* 2023; 24(22). https://doi.org/10.3390/ijms242216095