The Journal of Rheumatology 2021:48;xxxxxxxxxx
doi:10.3899/jrheum.200364
First Release December 1 2020

The Journal of Rheumatology

# Multicenter Validation of the DETAIL Questionnaire for the Screening of Spondyloarthritis in Patients With Inflammatory Bowel Diseases

Devis Benfaremo[1], Michele Maria Luchetti[1], Marco Di Carlo[1], Bruno Laganà[2], Andrea Picchianti-Diamanti[2], Francesco Carubbi[3], Roberta Pica[4], Maria Sole Chimenti[5], Roberto Lorenzetti[6], Palma Scolieri[7], Vincenzo Bruzzese[7], Antonio Benedetti[1], Roberta Ramonda[8], Roberto Giacomelli[3], Fausto Salaffi[1], and Armando Gabrielli[1], on behalf of the GRADES-IBD Study Group

***ABSTRACT.*** ***Objective.*** Spondyloarthritis (SpA) is among the most frequent extraintestinal manifestations of inflammatory bowel diseases (IBD). In this study, we aimed to validate the DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire in a multicenter cohort of patients with IBD enrolled at 11 gastroenterology units.

***Methods.*** From October 2018 to March 2019, consecutive adult patients with IBD, either Crohn disease or ulcerative colitis, independently filled out the DETAIL questionnaire in the outpatient waiting room. Within 2 weeks a blinded rheumatologist assessed all the patients, irrespective of the DETAIL results, and classified them to be affected or not by SpA. The performance of the questions was evaluated through Bayesian analysis.

***Results.*** Overall, 418 patients with IBD filled out the DETAIL questionnaire. Upon rheumatological evaluation, 102 (24.4%) patients received a diagnosis of SpA. Of the 6 questions, the best performances were found in question 6 [positive likelihood ratio (LR)+ 3.77], reporting inflammatory back pain at night, and in question 3 (LR+ 3.31), exploring Achilles enthesitis. The presence of back pain lasting > 3 months (LR+ 2.91), back pain with inflammatory features (LR+ 2.55), and a history of dactylitis (LR+ 2.55), also showed a fairly good performance, whereas a history of peripheral synovitis was slightly worse (LR+ 2.16). The combination of at least 3 questions answered affirmatively yielded a posttest probability of SpA of 80% or more. The presence of alternative diagnoses, such as osteoarthritis or fibromyalgia, represented a minor confounder.

***Conclusion.*** The DETAIL questionnaire is a useful tool for the early detection of SpA in IBD.

*Key Indexing Terms*: Crohn disease, inflammatory bowel diseases, spondyloarthritis, ulcerative colitis

*[1]D. Benfaremo, MD, M.M. Luchetti, MD, M. Di Carlo, MD, F. Salaffi, MD, PhD, A. Gabrielli, MD, A. Benedetti, MD, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Ancona; [2]B. Laganà, MD, A. Picchianti-Diamanti, MD, PhD, Department of Clinical and Molecular Medicine, S. Andrea University Hospital, "Sapienza" University, Rome; [3]F. Carubbi, MD, PhD, R. Giacomelli, MD, PhD, Rheumatology Unit, University Hospital "S. Salvatore", Department of Clinical and Biotechnologic Sciences, University of L'Aquila; [4]R. Pica, MD, UOS Gastroenterologia Territoriale, ASL Roma 2, Rome; [5]M.S. Chimenti, MD, UOC Reumatologia, Dipartimento di Medicina dei Sistemi, Università di Tor Vergata, Roma; [6]R. Lorenzetti, MD, UOC Gastroenterologia, Polo Ospedaliero Nuovo Regina Margherita - S.Spirito, Rome; [7]P. Scolieri, MD, V. Bruzzese, MD, UOC Medicina Interna e Reumatologia, Polo Ospedaliero Nuovo Regina Margherita - S.Spirito, Rome; [8]R. Ramonda, MD, PhD, UOC di Reumatologia, Dipartimento di Medicina DIMED, Università di Padova, Italy.*

*D. Benfaremo and M.M. Luchetti contributed equally to this manuscript as first authors. F. Salaffi and A. Gabrielli contributed equally to this manuscript as senior authors.*

*Address correspondence to Dr. M. Luchetti, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche Via Tronto 10/A 60126 Ancona, Italy. Email: m.luchetti@staff.univpm.it.*

*Accepted for publication July 3, 2020*

Inflammatory bowel disease–associated spondyloarthritis (SpA/IBD) is a systemic disease characterized by chronic inflammation of both the gastrointestinal tract and the musculoskeletal (MSK) system[1]. IBD, namely Crohn disease (CD) and ulcerative colitis (UC), are among the most frequent extraarticular complications that may occur in patients with spondyloarthirits (SpA), and similarly, arthritis is the most frequent extraintestinal manifestation in IBD and may develop before, simultaneously with, or after the diagnosis of overt intestinal disease[2].

The spectrum of the clinical features of the inflammatory articular involvement in IBD is broad, showing patterns of pure spinal involvement [axial SpA (axSpA), including both ankylosing spondylitis (AS) and nonradiographic axial SpA (nr-axSpA)] and patterns of exclusive peripheral arthritis and/or enthesitis[3].

The prevalence of SpA in patients with IBD ranges from 4% to 23% based on different studies[1]. A previous systematic review estimated that axSpA affects 13% of patients with IBD, with 10% as isolated sacroiliitis or nr-axSpA and with 3% as overt AS, whereas peripheral arthritis affects approximately 13% of IBD patients[4]. Additionally, a recent study with a long follow-up

reported that 20 years after IBD diagnosis, the prevalence of AS was 4.5% and of axSpA 7.7%, whereas 1 out of 4 patients developed peripheral SpA[5,6]. Importantly, the prevalence of axial involvement may be underestimated in patients with IBD, since subclinical sacroiliitis has been observed in approximately 16% of patients with IBD[7,8].

Despite the well-known relationship between gut and joint inflammation, the availability of the Assessment of SpondyloArthritis international Society (ASAS) classification criteria[9] and the more common use of accurate diagnostic techniques, such as magnetic resonance imaging (MRI) and ultrasonography (US), the diagnostic delay of SpA/IBD is still important. This is especially valid for patients with axial involvement, in which the diagnostic delay ranges from 5 to 10 years[10,11,12]. The reasons for such a delay are various, from clinicians not always querying patients about joint complaints, to patients themselves underreporting symptoms often misinterpreted as nonspecific mechanical joint or back pain[13].

The presence of such an unfavorable diagnostic delay, which often translates into a serious effect on the ability to work, social participation, and several other domains of quality of life[14,15], drives the need for a proper screening strategy. For example, the availability of accurate biomarkers could be useful to earlier intercept the onset of disease. However, to date, the quest for biomarkers in SpA/IBD has been largely unsatisfactory[16]. A dedicated referral strategy is another tool that could be implemented for such a task. Although during the last decade, several referral models for axSpA have been proposed[17,18,19], only a few have been specifically dedicated to SpA/IBD[20,21]. Additionally, most of these strategies focus on axial disease and do not adequately consider peripheral manifestations. Keeping in mind these issues, we recently developed and preliminarily validated a new self-administered screening tool, called the DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire, to recognize signs and/or symptoms of peripheral and/or axial inflammatory involvement in patients suffering from IBD not previously diagnosed as having SpA[22].

In this multicenter study, conducted at 11 tertiary referral hospitals located in Italy, we aimed to further validate the DETAIL questionnaire in an independent cohort of patients with IBD.

## MATERIALS AND METHODS

*DETAIL questionnaire development and preliminary validation*. Briefly, the DETAIL instrument has been developed as follows. In May 2016, the authors (DB, MML, MDC, and FS) identified a list of items from the already existing referral models for axSpA, with the goal of developing a 5- to 8-item questionnaire with dichotomous answers to be filled in quickly in the waiting room of the gastroenterology unit; the questionnaire should be easy to understand and require no laboratory or imaging tests. After the elimination of duplicates, composite questions, and items requiring special equipment or tools, a list of 30 items was drawn up. From June to October 2016, there were 95 experts in the field of SpA or IBD who rated the importance of each of the 30 items/questions for the detection of signs or symptoms of articular or spinal inflammation. Items were retained in the DETAIL questionnaire if they satisfied at least a mean score of 2 on a 0–3 Likert scale, and if they were rated as quite relevant or very relevant by at least 70% of the experts. The questions that satisfied the criteria for inclusion in the final questionnaire (frequency > 70% and mean relevance score > 2.0) were 6.

In October 2016, the final version of the DETAIL questionnaire, composed of the 6 top-rated items, was available (Table 1). The English version was translated to Italian, and then translated back to English by a native English speaker.

Thereafter, from October 2016 to April 2017, pilot testing was conducted at 3 gastroenterology units. In the preliminary validation, the DETAIL questionnaire showed good overall accuracy for the referral of patients with IBD. In particular, among the 6 items, the best positive likelihood ratio (LR+) was found in question 2 (LR+ 3.82), exploring dactylitis, and in questions 6 (LR+ 3.82) and 5 (LR+ 3.40), both of which explored inflammatory low back pain. Enthesitis (question 3, LR+ 2.87) and peripheral synovitis (question 1, LR+ 2.81) gave similar results, while question 4, exploring the duration of low back pain, resulted in the worst performance (LR+ 1.99)[22].

*Multicenter validation*. The present study was conducted at 11 tertiary referral centers for IBD, all in Italy. The inclusion criteria were as follows: patients with a diagnosis of IBD (according to the validated criteria[23,24]), > 18 years of age, without a previous diagnosis of SpA, and able to read and understand the Italian language. Subjects suffering from active cancer or lymphoproliferative disease, uncontrolled diabetes, unstable ischemic heart disease or congestive heart failure, acute renal failure, and those already diagnosed with inflammatory or crystal-induced arthropathies (including gout and calcium pyrophosphate dihydrate deposition disease) were excluded.

Patients were enrolled consecutively and asked to fill in the questionnaire in paper format before their gastroenterology visit. The study was explained by a specially trained nurse who also collected informed consent and answered the patients' questions. Thereafter, within 2 weeks from the completion of the questionnaire, a trained rheumatologist assessed all the patients, irrespective of and blinded to all the answers given to the DETAIL questions. The rheumatologic assessment was conducted according to a standard protocol and included a complete history, physical examination (tender and swollen joint counts on 68 and 66 joints, respectively, cervical rotation, tragus-to-wall distance, lumbar lateral flexion, modified Schober test, and intermalleolar distance), and laboratory assessment (acute-phase reactants, rheumatoid factor, antinuclear antibody, anticyclic citrullinated peptide, and HLA-B27, if needed). Radiographs, MRI, and US were performed if needed. The rheumatologists were required to confirm that patients with a clinical diagnosis of SpA also fulfilled the ASAS criteria[9], and, if appropriate, to diagnose the presence of other MSK disorders.

The study was approved by the institutional review board of

*Table 1*. The DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire for the screening of spondyloarthritis in patients with inflammatory bowel diseases.

| Questions | Yes | No |
|---|---|---|
| 1. Have you ever had a finger or a toe and/or another joint swollen and painful for no apparent reason? | | |
| 2. Occasionally, has an entire finger or toe become swollen, making it look like a "sausage"? | | |
| 3. Have you had pain in your heels? | | |
| 4. Have you ever had back pain lasting at least 3 months that was not injury-related? | | |
| 5. Do you have low back pain in the morning and/or after resting that improves with exercise? | | |
| 6. Do you wake up at night because of low back pain? | | |

the coordinating center (Comitato Etico Regionale delle Marche, n°20170206/5362) and by all the local ethics committees. The study was conducted in compliance with the principles of the Declaration of Helsinki. All patients were requested to sign a written informed consent.

*Statistical analysis*. Baseline demographic and clinical characteristics were recorded for all patients and transferred to an anonymous database. Mode imputation was used to handle missing data.

The performance of the DETAIL questionnaire was evaluated through the calculation of the posttest probability of disease. The posttest probability evaluation of a screening questionnaire is allowed by the knowledge of sensitivity, specificity, and the pretest probability (the prevalence of the disorder). In this study, the posttest probability was calculated using the Bayesian analysis model method, defining for each item of the questionnaire the LR+, and with graphic representation using Fagan nomogram. In this nomogram, a straight line drawn from a patient's pretest probability of disease through the total LR+ of the test (given by the LR+ product of the questions answered as "yes" in the questionnaire) will intersect with the posttest probability of disease on the right axis.

## RESULTS

*Patients*. From October 2018 to March 2019, 418 consecutive adult patients with IBD (211 female; 203 with CD, 209 with UC, 6 with indeterminate colitis; mean age 49.7 ± 14.4 yrs; and median duration of IBD of 10 yrs) independently filled out the DETAIL questionnaire in the waiting room of the gastroenterology unit outpatient clinics.

Upon rheumatologic assessment, 102 (24.4%) patients fulfilling the ASAS criteria were classified as SpA/IBD (Figure 1). This percentage represents the prevalence of SpA in our IBD cohort and therefore our pretest probability.

Patients' demographic and clinical characteristics are summarized in Table 2. There were no differences in the 2 groups, except for a higher proportion of women in the SpA/IBD cohort (60.8% vs 47.2%) and a slightly higher number of patients with SpA/IBD taking corticosteroids. Among patients with SpA/IBD, the median duration of joint complaints was 5 years (min 0, max 30). Fifty-eight patients (56.9%) were classified as having axSpA, with (18 patients) or without concomitant peripheral involvement, while 44 (43.1%) subjects with arthritis and/or enthesitis and/or dactylitis were classified as peripheral SpA. Among these patients, enthesitis was present in 26 patients (25.5%), whereas dactylitis was present only in 3 patients (3%). Concomitant fibromyalgia (FM) was present in 4 (4%) patients with SpA/IBD.

With regard to SpA disease activity, the mean Ankylosing Spondylitis Disease Activity Score (ASDAS) score was 3.0 ± 1.2 and the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 4.3 ± 2.0; mean C-reactive protein (CRP) levels were 1.0 ± 1.5 mg/dL.

*Alternative diagnoses*. Among IBD patients without SpA, 184 patients (58.2%) reported MSK complaints. The median number of affirmative responses to the DETAIL questions in this group was 1 (min 0, max 6). The most frequent alternative diagnosis was represented by osteoarthritis (OA; 142 patients, 33.9% of the whole cohort), in particular lumbar spine OA in 65 patients and peripheral OA in 77 subjects. In 22 patients (5.2% of the whole cohort), a diagnosis of FM was made. Ten participants had isolated tendinitis, 8 received a diagnosis of a specific muscle and joint pain, 1 had gout, and 1 had primary Raynaud phenomenon (data not shown).

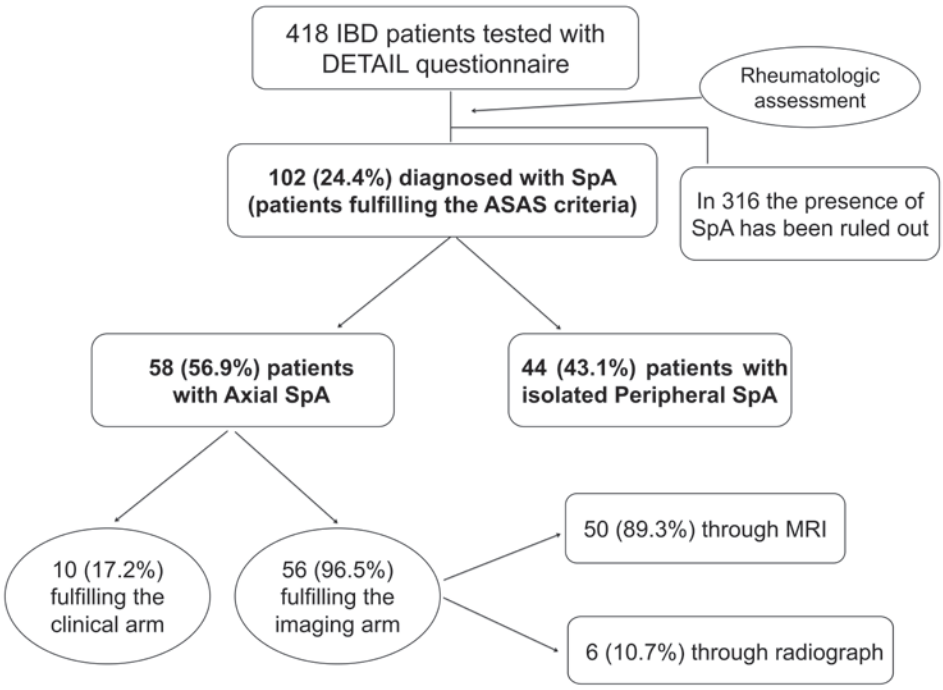


*Figure 1*. Flow chart showing the characteristics of the patients with IBD diagnosed with SpA. DETAIL: DETection of Arthritis in Inflammatory boweL diseases; IBD: inflammatory bowel diseases; MRI: magnetic resonance imaging; SpA: spondyloarthritis.

*Table 2.* Clinical and demographic characteristics of patients with IBD according to the diagnosis of SpA.

| | SpA/IBD, n = 102 | IBD Without SpA, n = 316 |
|---|---|---|
| Type of IBD, n (%) | | |
| CD | 54 (52.9) | 149 (47.2) |
| UC | 45 (44.1) | 164 (51.8) |
| IC | 3 (3.0) | 3 (1.0) |
| Female, n (%) | 62 (60.7) | 149 (47.1) |
| Age at inclusion, yrs, mean ± SD | 50 ± 12.5 | 49.5 ± 14.9 |
| IBD duration, yrs, median (min ÷ max) | 10 (0 ÷ 40) | 10 (0 ÷ 52) |
| Duration of joint symptoms, yrs, median (min ÷ max) | 5 (0 ÷ 30) | 2 (0 ÷ 35) |
| Concomitant psoriasis | 5 (4.9) | 9 (2.8) |
| IBD classification[a] | | |
| Localization CD, n (%) | | |
| L1 (ileal) | 23 (42.5) | 52 (34.9) |
| L2 (colonic) | 6 (11.1) | 21 (14.2) |
| L3 (ileocolonic) | 20 (37.1) | 67 (45.1) |
| L4 (isolated upper disease) | 3 (5.6) | 4 (2.7) |
| L1–3 + L4 | 2 (3.7) | 5 (1.2) |
| Behavior CD, n (%) | | |
| B1 (nonstricturing, nonpenetrating) | 28 (51.8) | 74 (49.7) |
| B2 (stricturing) | 17 (31.5) | 50 (33.5) |
| B3 (penetrating) | 3 (5.6) | 14 (9.4) |
| B2 + B3 | 6 (11.1) | 11 (7.4) |
| P (perianal disease) | 3 (5.6) | 12 (8.0) |
| Extension UC, n (%) | | |
| E1 (ulcerative proctitis) | 5 (11.1) | 14 (8.5) |
| E2 (left-sided UC) | 13 (28.9) | 73 (44.5) |
| E3 (extensive UC) | 27 (60.0) | 77 (47.0) |
| Current medication use, n (%) | | |
| 5-ASA[b] | 45 (44.1) | 141 (44.6) |
| Steroids (topical and oral) | 12 (11.7) | 18 (5.7) |
| Immunosuppressants[c] | 8 (7.8) | 24 (7.6) |
| Infliximab | 14 (13.7) | 67 (21.2) |
| Adalimumab | 19 (18.6) | 40 (12.6) |
| Golimumab | 3 (2.9) | 6 (1.9) |
| Ustekinumab | 3 (2.9) | 6 (1.9) |
| Vedolizumab | 8 (7.8) | 28 (8.9) |
| No therapy | 11 (10.8) | 30 (9.5) |
| SpA characteristics | | NA |
| axSpA[d], n (%) | 58 (56.9) | |
| Isolated peripheral SpA, n (%) | 44 (43.1) | |
| BASDAI, mean ± SD | 4.3 ± 2.0 | |
| ASDAS-CRP, mean ± SD | 3.0 ± 1.2 | |
| CRP, mg/dL, mean ± SD | 1.0 ± 1.5 | |

[a] According to the Montreal classification. [b] Mesalazine, sulfasalazine, balsalazide. [c] Azathioprine, 6-mercaptopurine, methotrexate. [d] With or without peripheral involvement. 5-ASA: 5-aminosalicylic acid; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score based on CRP; axSpA: axial spondyloarthritis; AZA: azathioprine; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CD: Crohn disease; CRP: C-reactive protein; IBD: inflammatory bowel disease; IC: indeterminate colitis; NA: not applicable; SpA: spondyloarthritis; UC: ulcerative colitis.

*DETAIL replies, feasibility, and acceptability*. The total number of replies to the DETAIL questions were as follows: (1) Question 1: 173 yes, 245 no; (2) Question 2: 63 yes, 355 no; (3) Question 3: 89 yes, 329 no; (4) Question 4: 163 yes, 255 no; (5) Question 5: 186 yes, 232 no; and (6) Question 6: 102 yes, 316 no.

The mean time to complete DETAIL was 46 ± 28 seconds, and it was fully completed by the vast majority of the subjects (< 2% of questionnaires had missing values). The majority of the subjects (85.2%) rated the questionnaire as easy to understand and complete.

The percentage of patients with or without SpA replying affirmatively to the single questions is shown in Figure 2A. Figure 2B shows the distribution of the total number of questions answered affirmatively in each group. In detail, among 102 patients with

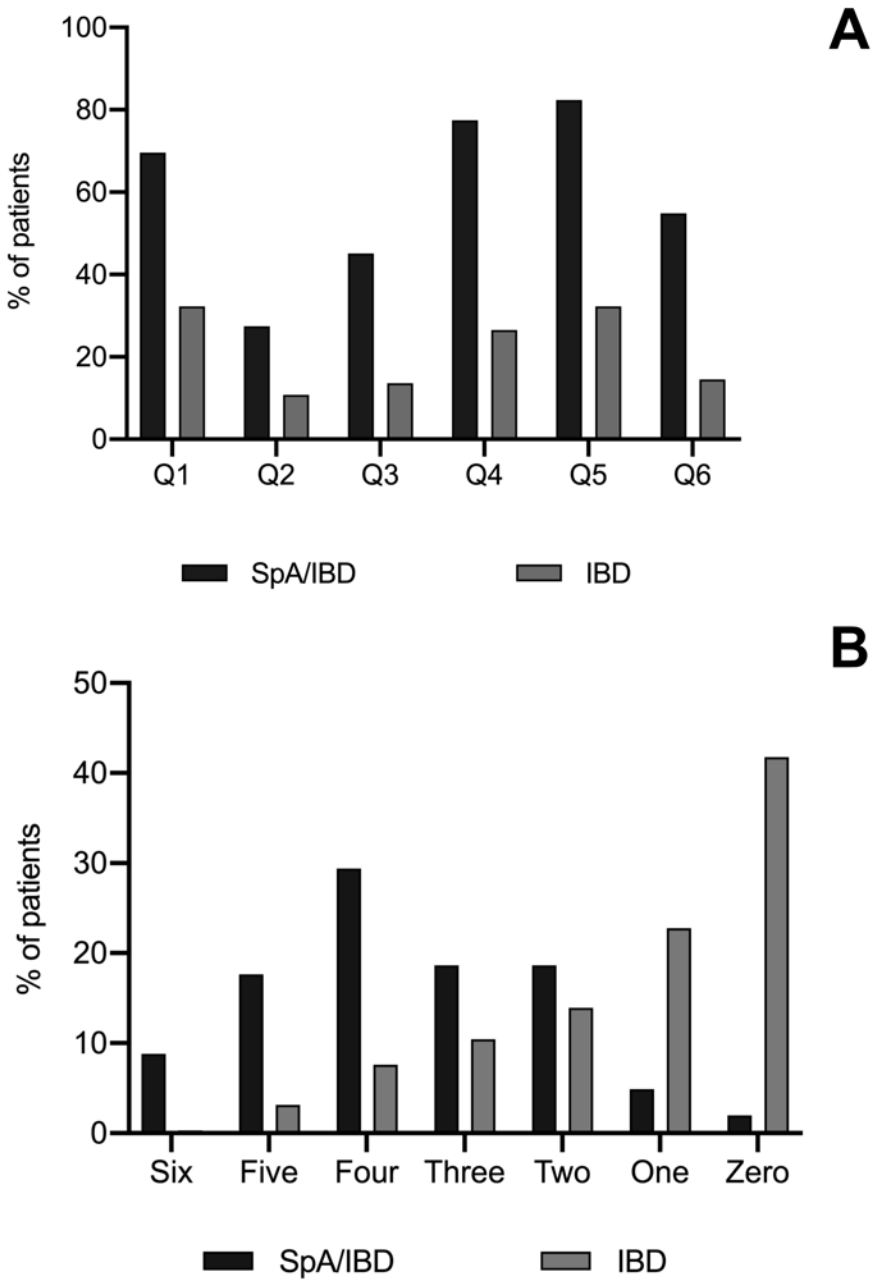


*Figure 2*. Distribution of the replies to the DETAIL questionnaire. (A) The percentage of patients with or without SpA answering affirmatively to each question [from question 1 (Q1) to question 6 (Q6)]. (B) The distribution of the total number of questions answered affirmatively in each group, from 6 questions to 0. DETAIL: DETection of Arthritis in Inflammatory boweL diseases; IBD: inflammatory bowel diseases; SpA: spondyloarthritis.

SpA/IBD, 9 answered 6 of 6 as yes, 18 answered 5 of 6 as yes, 30 answered 4 of 6 as yes, 19 answered 3 of 6 as yes, 19 answered 2 of 6 as yes, 5 answered 1of 6 as yes, and 2 answered 0 of 6 as yes.

Patients with IBD without concomitant SpA represented the majority of the cohort (316, 75.6%). Of these, 132 answered 0 of 6 as yes, 72 answered 1 of 6 as yes, 44 answered 2 of 6 as yes, 33 answered 3 of 6 as yes, 24 answered 4 of 6 as yes, 10 answered 5 of 6 as yes, and 1 answered 6 of 6 as yes on the DETAIL questionnaire.

*Analysis of the DETAIL performance*. As shown in Table 3, applying the Bayesian analysis to the 6 questions of DETAIL, the best performances in discriminating patients affected or not by SpA were found in question number 6 (LR+ 3.77, 95% CI 2.74–5.19), reporting inflammatory low back pain at night, and in question number 3 (LR+ 3.31, 95% CI 2.33–4.71), exploring Achilles enthesitis.

The other 2 questions exploring the duration of low back pain (question 4: LR+ 2.91, 95% CI 2.36–3.60) and its inflammatory

*Table 3.* Sensitivity, specificity, positive and negative predictive values, likelihood ratios, and posttest probabilities of the 6 items of the DETAIL questionnaire.

| Questions | Sensitivity, % (95% CI) | Specificity, % (95% CI) | Positive Predictive Value, % (95% CI) | Negative Predictive Value, % (95% CI) | Positive Likelihood Ratio (95% CI) | Negative Likelihood Ratio (95% CI) |
|---|---|---|---|---|---|---|
| 1. Have you ever had a finger or a toe and/or another joint swollen and painful for no apparent reason? | 69.6 (59.7–78.3) | 67.7 (62.2–72.8) | 41.0 (36.1– 46.0) | 87.3 (83.6–90.3) | 2.16 (1.78–2.65) | 0.45 (0.33–0.61) |
| 2. Occasionally, has an entire finger or toe become swollen, making it look like a "sausage"? | 27.4 (19.0–37.1) | 89.2 (85.2–92.4) | 45.1 (34.4–56.3) | 79.2 (77.0–81.2) | 2.55 (1.63–3.99) | 0.81 (0.72–0.92) |
| 3. Have you had pain in your heels? | 45.1 (35.2–55.2) | 86.3 (82.1–89.9) | 51.6 (42.9–60.3) | 82.9 (80.2–85.3) | 3.31 (2.33–4.71) | 0.64 (0.53–0.76) |
| 4. Have you ever had back pain lasting at least 3 months that was not injury related? | 77.4 (68.1–85.1) | 73.4 (68.1–78.2) | 48.4 (43.2–53.7) | 90.9 (87.5–93.5) | 2.91 (2.36–3.60) | 0.31 (0.21–0.44) |
| 5. Do you have low back pain in the morning and/or after resting that improves with exercise? | 82.3 (73.5–89.1) | 67.7 (62.2–72.8) | 45.1 (40.6–49.7) | 92.2 (88.5–94.7) | 2.55 (2.12–3.06) | 0.26 (0.17–0.40) |
| 6. Do you wake up at night because of low back pain? | 54.9 (44.7–64.7) | 85.4 (81.6–89.1) | 54.9 (46.9–62.6) | 85.4 (82.5–87.9) | 3.77 (2.74–5.19) | 0.53 (0.42–0.66) |

DETAIL: DETection of Arthritis in Inflammatory boweL diseases.

features (question 5: LR+ 2.55, 95% CI 2.12–3.06) also demonstrated a fairly good performance for the detection of patients with axSpA.

A history of dactylitis and the presence of signs and symptoms of peripheral synovitis had an overall slightly worse performance (question 2: LR+ 2.55, 95% CI 1.63–3.99; and question 1: LR+ 2.16, 95% CI 1.78–2.65, respectively).

*Application of the DETAIL questionnaire*. The DETAIL instrument is easily applied using Fagan nomogram representation. The product of LR+ of each affirmative answer should be used in order to obtain the probability of SpA in each individual patient, starting from their pretest probability (the prevalence of the disease). A test is usually considered very useful (i.e., having a large effect on the pretest probability), if LR+ is equal to 10 or more. For the DETAIL questionnaire, the combination of 3 or more different questions answered affirmatively yields an LR+ of at least 14 (questions 1, 2, and 5). Applying this LR+ to our prevalence of the disease, we obtained a posttest probability of 81.9%, which is high enough to warrant referral (Figure 3).

The development of a DETAIL mobile app for smartphones, which is ongoing, will allow the automatic and immediate calculation of the posttest probability of disease as soon as the patient answers the questions. Thus, the posttest probability will be readily available on-screen to the clinician, who will see a highlighted value to mean that referral is strongly indicated, if at least 3 affirmative answers have been given.

## DISCUSSION

The aim of this study was to validate a recently developed questionnaire for the early detection of signs and symptoms of SpA in patients with IBD that showed good screening properties in a preliminary study[22].

In this multicenter work, the DETAIL instrument was confirmed to be an easy and powerful tool for rheumatologic referral of IBD patients with joint complaints. Briefly, among the 418 IBD patients who underwent screening with the DETAIL instrument, 102 were diagnosed with SpA/IBD (58 with axSpA and 44 with isolated peripheral SpA), for a pooled prevalence of SpA of 24%, further confirming that articular involvement is among the most frequently reported extraintestinal manifestations in IBD[1,12]. In our cohort, patients with SpA/IBD had a median diagnostic delay of 5 years, and a high disease activity according to mean ASDAS score. Among patients with SpA/IBD who have been diagnosed with axSpA, 1 out of 3 also had a concomitant peripheral involvement.

The DETAIL questionnaire is composed of 6 questions querying both axial and peripheral joint symptoms. Overall, the questions exploring axial disease (items 4–6) have a better accuracy compared to those that question peripheral involvement. The items exploring enthesitis (question 3) and dactylitis (question 2) are highly specific, though not sensitive, reflecting their lower prevalence in our cohort (6% and < 1% of the whole cohort, respectively). Compared to a disease in the same

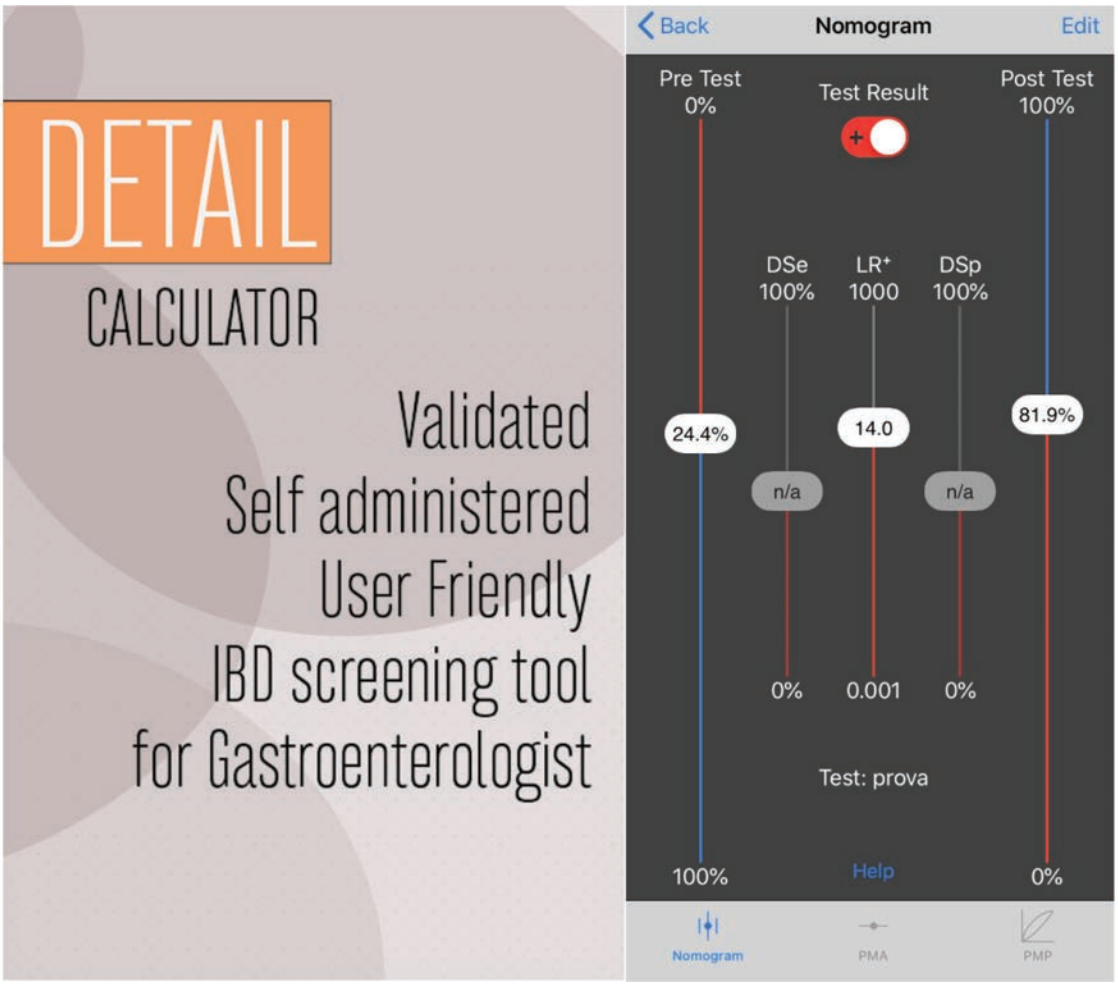


*Figure 3.* Application of the DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire; an example of an application of the nomogram in the calculation of the posttest probability. The likelihood ratio product of the 3 questions about peripheral arthritis (question 1), dactylitis (question 2), and back pain with inflammatory features (question 5) is 14, with resultant posttest disease probability of 81.9%. DSe: diagnostic test sensitivity; DSp: diagnostic test specificity; LR+: positive likelihood ratio; N/A: not applicable.

spectrum, such as psoriatic arthritis (PsA), the referral of IBD patients with MSK involvement is still suboptimal, but the best strategy to achieve an earlier diagnosis of SpA/IBD has not been determined. For example, establishing a multidisciplinary team that provides a simultaneous evaluation improves the global management of both PsA and SpA/IBD patients[12,25,26,27], but it is also true that such a strategy may not be feasible in all settings, considering limitations in terms of time and resources. An appropriate strategy should thus optimize the cooperation between gastroenterologists and rheumatologists, referring to each other only the patients with a high probability of disease.

Whereas several questionnaires have been proposed and validated as screening tools for PsA[28,29], for SpA/IBD there is a lack of effective instruments. The Toronto Axial Spondyloarthritis Questionnaire in Inflammatory Bowel Disease was developed in 2013[20], but it was thought to be administered only to patients who have ever had chronic back pain or stiffness persisting for ≥ 3 months and, to our knowledge, a formal validation study has not been conducted yet. Queiro, *et al* proposed 2 different 3-question surveys in a preliminary study, one exploring axial involvement and one peripheral arthritis, a strategy showing promising properties[21].

The DETAIL questionnaire has several important advantages. The strengths of this tool are its ease of use, feasibility, and accuracy. The questionnaire can be easily filled in by the patient while waiting for their gastroenterological visit since it is composed of 6 simple questions and does not require any laboratory or imaging tests. Indeed, the use of the Bayesian method allows the clinician to obtain an estimate of the posttest probability of the patient having SpA in a few seconds. The proposed cutoff of 3 affirmative answers out of 6 is not intended to be used categorically, as the results of this screening questionnaire are the first step within a referral strategy that aims to increase the chances that patients with IBD seen by the rheumatologist are affected by SpA and, thus, even referral of patients with fewer than 3 questions answered positively may be acceptable in some cases. Finally, since the use of Fagan nomogram in clinical practice is impractical, the availability of a smartphone app will make

such a tool much easier for both patients and physicians to use.

The ability of the DETAIL to intercept patients at high risk for inflammatory axial involvement is important, as almost half of patients with IBD may report back pain, most of the time nonspecific or mechanical in nature, during the course of the disease[5]. In fact, the early identification of patients affected by axSpA allows earlier treatment with effective therapies such as biologic drugs[30]. Compared to the other available questionnaires, the added value of the DETAIL questionnaire is the presence of 3 items exploring peripheral joint disease, including enthesitis and dactylitis, which are often easily overlooked by clinicians but constitute a significant cause of morbidity in these patients.

The DETAIL instrument has some potential limitations. First, it may not be able to discriminate between inflammatory, mechanic, or neuropathic sources of pain. As such, symptoms from noninflammatory MSK diseases may represent minor confounders. Of note, patients with OA usually answered affirmatively to only a few questions (< 3), thereby restricting their immediate referral to the rheumatologist. Conversely, FM should be a concern in every patient who reports widespread pain, since this comorbidity may affect up to 30% of patients with IBD[31]. In this subgroup, the DETAIL questionnaire is likely less useful. However, even if they are referred, the rheumatologist should be able to discriminate between inflammatory pain and central sensitization to make a proper diagnosis[32]. Concomitant psoriasis is another potential confounder, since joint symptoms in this population of IBD patients may indicate the presence of PsA, whether known or not. Although it may reduce the specificity of the questionnaire, the referral of some patients with PsA could be expected and thus they should be managed accordingly.

The study has some limitations as well. First, the clinical assessment of SpA may reflect the local clinical practice, as it was made by different rheumatologists in various tertiary referral centers. These issues were addressed by using (1) blinding, (2) a standardized procedure for the rheumatological assessment, and (3) ASAS classification criteria for the diagnosis of SpA. Second, it is possible that patients with subclinical sacroiliitis may have been misclassified, since our screening strategy is based on symptoms and MRI was not systematically performed on all subjects. In this regard, we cannot exclude the risk of overdiagnosis, given the known limitations of bone marrow edema in the definition of active sacroiliitis.

In conclusion, we developed and validated the DETAIL instrument, a new screening tool for the detection of SpA, in a large multicenter IBD cohort. DETAIL is a 6-item questionnaire that allows the immediate calculation of the probability of having SpA/IBD and thus will surely represent an important instrument for the screening and rheumatologic referral of patients with IBD.

## ACKNOWLEDGMENT

We are grateful to all the patients who kindly agreed to participate in this study. We also would like to acknowledge the Società Italiana di Gastro-Reumatologia (SIGR) for its help and assistance in the constitution of the multidisciplinary network.

## REFERENCES

1. Fragoulis GE, Liava C, Daoussis D, Akriviadis E, Garyfallos A, Dimitroulas T. Inflammatory bowel diseases and spondyloarthropathies: From pathogenesis to treatment. World J Gastroenterol 2019;25:2162-76.
2. Rodríguez-Reyna TS, Martínez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. World J Gastroenterology 2009;15:5517-24.
3. D'Incà R, Podswiadek M, Ferronato A, Punzi L, Salvagnini M, Sturniolo GC. Articular manifestations in inflammatory bowel disease patients: a prospective study. Dig Liver Dis 2009;41:565-9.
4. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The prevalence and incidence of axial and peripheral spondyloarthritis in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 2017;11:631-42.
5. Ossum AM, Palm Ø, Lunder AK, Cvancarova M, Banitalebi H, Negård A, 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;12:96-104.
6. Ossum AM, Palm Ø, Cvancarova M, Solberg IC, Vatn M, Moum B, et al. Peripheral arthritis in patients with long-term inflammatory bowel disease. Results from 20 years of follow-up in the IBSEN study. Scand J Gastroenterol 2018;53:1250-56.
7. Leclerc-Jacob S, Lux G, Rat AC, Laurent V, Blum A, Chary-Valckenaere I, et al. The prevalence of inflammatory sacroiliitis assessed on magnetic resonance imaging of inflammatory bowel disease: a retrospective study performed on 186 patients. Aliment Pharmacol Ther 2014;39:957-62.
8. Kelly OB, Li N, Smith M, Chan J, Inman RD, Silverberg MS. The prevalence and clinical associations of subclinical sacroiliitis in inflammatory bowel disease. Inflamm Bowel Dis 2019;25:1066-71.
9. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-83.
10. Feldtkeller E, Khan M, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int 2003;23:61-6.
11. Conigliaro P, Chimenti MS, Ascolani M, Triggianese P, Novelli L, Onali S, et al. Impact of a multidisciplinary approach in enteropathic spondyloarthritis patients. Autoimmun Rev 2016;15:184-90.
12. Luchetti MM, Benfaremo D, Bendia E, Bolognini L, Fava G, Marini F, 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.
13. Luchetti MM, Benfaremo D, Ciccia F, Bolognini L, Ciferri M, Farinelli A, et al. Adalimumab efficacy in enteropathic spondyloarthritis: a 12-mo observational multidisciplinary study. World J Gastroenterol 2017;23:7139-49.
14. Di Carlo M, Lato V, Di Matteo A, Carotti M, Salaffi F. Defining functioning categories in axial Spondyloarthritis: the role of the ASAS Health Index. Rheumatol Int 2017;37:713-8.
15. Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. Health Qual Life Outcomes 2009;7:25.
16. Benfaremo D, Luchetti MM, Gabrielli A. Biomarkers in inflammatory bowel disease-associated spondyloarthritis: state of the art and unmet needs. J Immunol Res 2019;2019:8630871.

17. Braun A, Gnann H, Saracbasi E, Grifka J, Kiltz U, Letschert K, et al. Optimizing the identification of patients with axial spondyloarthritis in primary care—the case for a two-step strategy combining the most relevant clinical items with HLA B27. Rheumatology 2013;52:1418-24.
18. Brandt HC, Spiller I, Song IH, Vahldiek JL, Rudwaleit M, Sieper J. Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. Ann Rheum Dis 2007;66:1479-84.
19. Poddubnyy D, Vahldiek J, Spiller I, Buss B, Listing J, Rudwaleit M, et al. Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol 2011;38:2452-60.
20. Alnaqbi KA, Touma Z, Passalent L, Johnson SR, Tomlinson GA, Carty A, et al. Development, sensibility, and reliability of the Toronto Axial Spondyloarthritis Questionnaire in inflammatory bowel disease. J Rheumatol 2013;40:1726-35.
21. Queiro R, Rodríguez-Caminero S, Riestra S, de Francisco R, Pérez-Martínez I, Ballina J. Performance of two screening questionnaires for inflammatory arthritis in patients with inflammatory bowel disease. Biomed Res Int 2018;2018:8618703.
22. Di Carlo M, Luchetti MM, Benfaremo D, Di Donato E, Mosca P, Maltoni S, et al. The DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire: development and preliminary testing of a new tool to screen patients with inflammatory bowel disease for the presence of spondyloarthritis. Clin Rheumatol 2018;37:1037-44.
23. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, 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;11:3-25.
24. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, 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;11:649-70.
25. Chimenti MS, Conigliaro P, Triggianese P, Canofari C, Cedola F, Onali S, et al. Use of synthetic and biological DMARDs in patients with enteropathic spondyloarthritis: a combined gastro-rheumatological approach. Clin Exp Rheumatol 2019;37:723-30.
26. Luchetti MM, Benfaremo D, Campanati A, Molinelli E, Ciferri M, Cataldi S, et al. Clinical outcomes and feasibility of the multidisciplinary management of patients with psoriatic arthritis: two-year clinical experience of a dermo-rheumatologic clinic. Clin Rheumatol 2018;37:2741-9.
27. Visalli E, Crispino N, Foti R. Multidisciplinary management of psoriatic arthritis: the benefits of a comprehensive approach. Adv Ther 2019;36:806-16.
28. Salaffi F, Di Carlo M, Luchetti MM, Di Donato E, Campanati A, Benfaremo D, et al. A validation study of the Simple Psoriatic Arthritis Screening (SiPAS) questionnaire to screen psoriasis patients for psoriatic arthritis. Clin Exp Rheumatol 2018;36:127-35.
29. Iragorri N, Hazlewood G, Manns B, Danthurebandara V, Spackman E. Psoriatic arthritis screening: a systematic review and meta-analysis. Rheumatology 2019;58:692-707.
30. Luchetti MM, Benfaremo D, Gabrielli A. Biologics in inflammatory and immunomediated arthritis. Curr Pharm Biotechnol 2017;18:989-1007.
31. Buskila D, Odes LR, Neumann L, Odes HS. Fibromyalgia in inflammatory bowel disease. J Rheumatol 1999;26:1167-71.
32. Di Carlo M, Becciolini A, Lato V, Crotti C, Favalli EG, Salaffi F. The 12-item Psoriatic Arthritis Impact of Disease questionnaire: construct validity, reliability, and interpretability in a clinical setting. J Rheumatol 2017;44:279-85.

**APPENDIX 1.** List of collaborators in the GRoup for the vAlidation of the DEtail in Spondyloarthritis-Inflammatory Bowel Disease (GRADES-IBD) Study Group: Valentina Marconi, Lucia Perini, Valentino Paci, Monia Ciferri, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Ancona, Italy; Laura Bolognini, Antonio Di Sario, Emanuele Bendia, Piergiorgio Mosca, Dipartimento Gastroenterologico e dei Trapianti, AOU Ospedali Riuniti di Ancona, Italy; Davide Giuseppe Ribaldone, Department of Surgical Sciences, University of Torino, Italy; Maria Chiara Ditto, S.C. Reumatologia, Città della Salute e della Scienza di Torino, Italy; Viktoriya Pavlych, Rheumatology Unit, University Hospital "S. Salvatore", Department of Clinical and Biotechnologic Sciences, University of L'Aquila, Italy; Angelo Viscido, Gianpiero Stefanelli, Gastroenterology Unit, University Hospital "S. Salvatore" Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy; Paola Conigliaro, UOC Reumatologia, Dipartimento di Medicina dei Sistemi, Università di Tor Vergata, Roma, Italy; Livia Biancone, UOC Gastroenterologia, Dipartimento di Scienze Mediche, Università di Tor Vergata, Roma, Italy; Pamela Polito, UOC di Reumatologia, Dipartimento di Medicina DIMED, Università di Padova, Italy; Renata D'Incà, UOC di Gastroenterologia, Azienda Ospedaliera di Padova, Italy; Luca Navarini, Unit of Allergology, Clinical Immunology and Rheumatology, Campus Bio-Medico University of Rome, Italy; Paola Balestrieri, Unit of Digestive Diseases, Campus Bio Medico University of Rome, Italy; Mariaelena Serio, Stefania Maltoni, Antonella Scarcelli, UOC Gastroenterologia ed Endoscopia Digestiva, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", Pesaro-Fano, Italy; Rita Girolimetti, Gabriele Frausini, UOC Medicina Interna, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", Pesaro-Fano, Italy; Flavia Baccini, UOC Malattie Apparato Digerente e Fegato, Ospedale S. Andrea, Roma, Italy; Paola Tomietto, Medicina Clinica, Azienda Sanitaria Universitaria Integrata di Trieste, Italy; Cinzia Tonello, SC Gastroenterologia, Azienda Sanitaria Universitaria Integrata di Trieste, Italy; Marco Fiorani, UOC Medicina, Ospedale Sandro Pertini, ASL Roma 2, Rome, Italy; Rebecca Marcasciano, UOC Medicina, Ospedale Sandro Pertini, ASL Roma 2, Rome, Italy.