Inflammatory bowel diseases and spondyloarthritis: a focus on female patients

C. Caranfil[1,2], G. Lorenzon[1], B. Barberio[2], R. Ramonda[3], E.V. Savarino[1,2], F. Zingone[1,2]

[1]Department of Surgery, Oncology, and Gastroenterology, University of Padova, Italy;
[2]Gastroenterology Unit, Azienda Ospedale - Università Padova, Italy;
[3]Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Italy

SUMMARY

Objective. Ulcerative colitis and Crohn's disease are chronic inflammatory diseases and represent the two most important types of inflammatory bowel diseases (IBD), while spondyloarthritis (SpA) comprises a heterogeneous group of systemic inflammatory chronic rheumatic diseases, including peripheral SpA and axial SpA. Joint manifestations are the most commonly observed extraintestinal manifestations, and they can precede or not the diagnosis of IBD. Notably, in women, misdiagnoses of IBD as irritable bowel syndrome and SpA as fibromyalgia are common, leading to delayed diagnoses, increased disease burden, and poorer prognoses. This narrative review emphasizes the critical role of diagnostic tools in facilitating early referrals of IBD patients with suspected SpA and *vice versa* to rheumatologists and gastroenterologists, respectively. Special attention is given to the multidisciplinary approach for more effective management of these conditions, particularly in female patients.

Methods. In this narrative review, we critically evaluated the literature on this topic, focusing on papers written in English that address female issues in IBD and SpA.

Results. IBD and SpA are chronic inflammatory disorders often occurring in the same patients. Female patients are often misdiagnosed, and this delay in diagnosis is associated with a higher disease burden and a poorer prognosis.

Conclusions. A multidisciplinary approach is needed to enable early referral between gastroenterologists and rheumatologists, as this means a better prognosis for patients with a reduction in the economic and social burden associated with IBD and SpA.

Key words: *Arthritis, crohn disease, ulcerative colitis, females.*

Reumatismo, 2024; 76 (3): 186-195

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases and represent the two most important types of inflammatory bowel diseases (IBD). While UC primarily affects the colon (1), CD can affect the entire gastrointestinal tract (2).

Spondyloarthritis (SpA) comprises a heterogeneous group of systemic inflammatory chronic rheumatic diseases, including peripheral SpA and axial SpA (axSpA), which can be further subdivided into radiographic axSpA, also known as ankylosing spondylitis (AS) with radiological signs of sacroiliitis, and non-radiographic SpA (nr-axSpA) (3).

In women, IBD and SpA are often misdiagnosed as irritable bowel syndrome (IBS) (4, 5) and fibromyalgia, respectively, which have a higher prevalence among the female population. Indeed, in women aged between 20 and 55 years, IBS and fibromyalgia are reported to be the most common causes of abdominal and musculoskeletal pain (6-9). As a result, diagnosis and treatments are delayed, leading to concerns about prognosis (10, 11). It is crucial to improve the knowledge of IBD and SpA to enhance these patients' quality of everyday life and reduce the economic and social burden associated with both of them (12).

To reach this goal, a multidisciplinary approach is suggested. In this narrative re-

Corresponding author:
Fabiana Zingone
Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy
E-mail: fabiana.zingone@unipd.it

view, we will focus on the diagnostic tools that can be useful for an early referral of IBD patients with suspicion of SpA and *vice versa* to rheumatologists and gastroenterologists, respectively, with specific regard to female patients.

EPIDEMIOLOGY

IBD is a golabally widespread disease with a prevalence of up to 0.5% of the general population in the Western world; both the incidence and prevalence of IBD are increasing in Asia and Eastern Europe (13-15). Women are more frequently affected than men (3.9 *versus* 3.0 million), and the number of prevalent cases is expected to increase in the coming years. The peak incidence of IBD, followed by a chronic relapsing course, usually occurs in the second to fourth decade of life, the most productive period of adulthood, when women usually dedicate themselves to childbearing (16, 17).

In up to 20-40% of cases, IBD can be associated with extraintestinal manifestations (EIMs), which can be defined as any inflammatory pathologies occurring outside the gastrointestinal tract in patients with IBD. These manifestations may arise either due to the extension or translocation of immune responses from the gut, or they may represent an independent inflammatory event perpetuated by IBD or share a common environmental predisposition with IBD (18).

Joint manifestations are the most commonly observed EIMs (8%) (19), and they can precede or not the diagnosis of IBD. In the Swiss Inflammatory Bowel Disease Cohort, peripheral arthritis and axial spondylitis were diagnosed before a diagnosis of IBD in 19.7% and 39.1% of patients, respectively (20). The cumulative incidence of spondyloarthropathy 10, 20, and 30 years after diagnosis of UC is 5%, 14%, and 22%, respectively (19). Being affected by IBD increases the likelihood of a diagnosis of axSpA by 21.4% (21). While r-axSpA usually begins in the third decade of life and affects men two times more than women, nr-axSpA, whose incidence increases over time, partly due to better recognition of the disease, affects both sexes equally (22, 23). However, female IBD patients have a higher risk of developing rheumatological manifestations in general (24). Algaba *et al.* confirmed that joint involvement in IBD is more common in women than in men (25), particularly for peripheral joint disease, which occurs in almost 67% of patients. However, there is no difference in the prevalence of CD- and UC-related peripheral arthritis, while men more often have axial involvement (26, 27). Figure 1 shows the spectrum of musculoskeletal manifestations in IBD female patients.

Likewise, the prevalence of IBD in SpA patients is higher than in the general population, ranging from 4% to 14% (28). In almost 70% of patients with AS or other forms of SpA, microscopic evidence of bowel inflammation is found, but only 7% develop CD (29). In the IBSEN study, which included IBD patients, the prevalence of AS was 4.5%, nr-axialSpA was 7.5%, inflammatory back pain (IBP) according to the Assessment of SpondyloArthritis International Society Group (ASAS) criteria was 11.5%, and chronic back pain was 46.8%, 20 years after the diagnosis; no significant differences were found between UC and CD patients (30). Compared to SpA patients without IBD, patients with IBD are less likely to be male, more likely

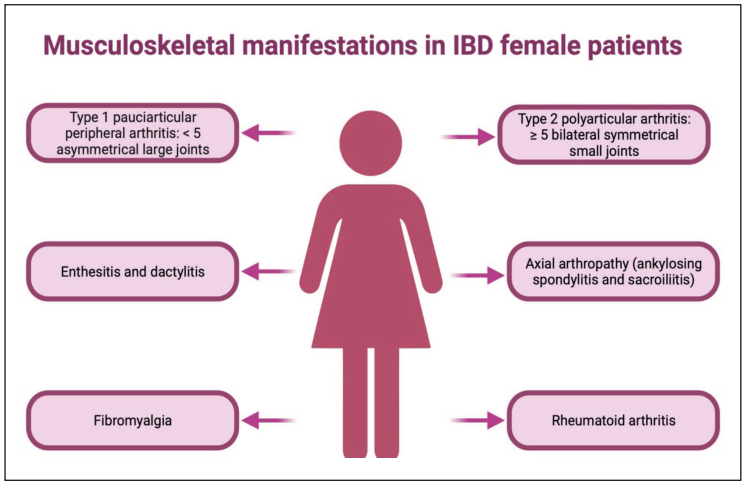

Figure 1 - Overview of the spectrum of musculoskeletal manifestations in female patients with inflammatory bowel diseases (IBD).

to have a delayed diagnosis, and more likely to report a family history of IBD (31). Compared to men, women have a higher prevalence of various articular and extra-articular manifestations (32, 33).

PATHOGENESIS

It is beyond the scope of this review to provide an in-depth insight into the pathogenesis of IBD and SpA. In short, environmental factors, genetic predisposition, and communication between organs *via* cellular traffic involving different types of cytokines are the most important factors leading to IBD and SpA. Subclinical intestinal inflammation may be present in many patients with SpA. The main hypothesis favoring the gut-joint axis is that the inflammatory process begins in the gut, where dysbiosis causes increased permeability and consequent immune activation (34). Dysbiosis of the gut microbiome is associated with IBD. This manifests as a reduction in microbial diversity, leading to an imbalance between potentially pathogenic and commensal microorganisms (35). There are two major theories to explain the development of arthritis associated with IBD concerning gut bacteria and the migration of gut lymphocytes into the joint, but both are not yet fully developed. In the first, the transgenic rat model of SpA-like disease with HLA-B27/human beta-2-microglubulin, a germ-free environment prevents the development of gut and joint disease, suggesting that bacterial exposure is necessary for the development of SpA in the proper genetic background. The second claims that T cells activated in the gut can infiltrate the synovium thanks to specific adhesion molecules, *e.g.*, $\alpha 4\beta 7$ and aEb7 and MadCAM-1, a mucosal vascular receptor, as identical T cell clones have been identified in the synovium and intestinal mucosa of a patient with SpA (36-38).

DIAGNOSIS

Who could benefit from an inflammatory bowel disease consultation?

Identifying individuals who could benefit from an IBD consultation involves considering various symptoms and markers. IBD diagnosis integrates clinical, biochemical, and fecal biomarkers, as well as endoscopic, histological, and radiological features (39). Common symptoms of IBD include chronic diarrhea, abdominal pain, weight loss, and rectal bleeding. About 30% of patients with IBD experience a silent disease (5). Symptoms like bloody diarrhea, tenesmus, urgency, and fecal incontinence are typical of UC. They depend on the extent and severity of the disease and can also be accompanied by nocturnal bowel movements and fatigue (40).

On the other hand, CD is clinically more insidious than UC. Diarrhea and abdominal pain are the main symptoms. They can be accompanied by fatigue, weight loss, fever, anemia, recurrent fistulae, or other perianal findings (ulcers or fissures). Hyperactive bowel sounds, nausea, and vomiting may be an expression of bowel obstructions in patients with stricturing disease. Indeed, there are four different phenotypes of CD: stricturing disease; penetrating disease due to fistulas between the bowel and other structures; inflammatory or non-stricturing, non-penetrating disease; and stricturing, penetrating disease (2). Due to these characteristics, CD is associated with a longer delay in diagnosis. In a Swiss IBD cohort, a difference of 5 months was found between CD and UC (9 months for CD *versus* 4 months for UC, $p<0.001$) (41). This discrepancy can be explained by the fact that the initial symptoms and signs of IBD can be non-specific and categorized as IBS (42). Another reason that may explain the delay in diagnosis of CD is that rectal bleeding, which is typical of UC, prompts these patients to consult their general practitioner earlier (43). For IBD, which is frequently misdiagnosed at all levels of healthcare, there is a 4-month delay in diagnosis between men and women. Gastrointestinal infections (29.5%) and functional gastrointestinal disorders (13.7%) are the most commonly misdiagnosed conditions. It is also assumed that functional gastrointestinal disorders occur more frequently in women (44).

Fecal calprotectin, a non-invasive marker of intestinal inflammation that reflects the migration of neutrophils through the inflamed bowel wall (45), is a very reliable test to rule out IBD. It has a sensitivity of 85.8% and a specificity of 91.7%, with a negative predictive value of 99.8% in primary care and 99.2% in secondary care. It is also important to note that fecal biomarkers may be somewhat less accurate in detecting endoscopic inflammation in CD in the small bowel or upper gastrointestinal tract disease than in patients with predominant or extensive colonic involvement (46). Between 21.2% and 70.7% of patients with SpA or AS exhibit elevated fecal calprotectin levels (45). Of note, a recent 14-year retrospective cohort study has shown that patients with AS have a statistically significant higher risk of developing IBS (47). Some clinical red flags can be very useful in clinical practice. Rheumatic patients with chronic diarrhea for more than 4 weeks, abdominal pain for more than 3 months, nocturnal diarrhea or abdominal pain, rectal bleeding (not due to hemorrhoids), perianal fistulas or abscesses, recurrent oral aphthosis, unexplained constitutional symptoms (weight loss, fever, anemia), or a family history of IBD should be referred to the gastroenterologist (27, 48). Danese *et al.* have developed a Red Flag Index to detect patients with CD at an early stage: a 21-item questionnaire with a minimum Red Flags Index score of at least 8 is highly predictive of CD diagnosis with a sensitivity and specificity of 0.94 (95% confidence interval 0.88-0.99) and 0.94 (95% confidence interval 0.90-0.97), respectively (42). A combined diagnostic strategy with fecal calprotectin leads to significantly improved diagnostic accuracy: sensitivity 100%, specificity 72%, positive predictive value = 21%, negative predictive value = 100% (49). Scott *et al.* developed a referral care pathway using the RAND/UCLA Appropriateness Method (50). In the presence of at least one major criterion, as shown in Figure 2, an advanced disease should be suspected, needing consultation with an IBD specialist (50). In the presence of at least two minor criteria (Figure 2), the patient should also be referred to an IBD specialist (50).

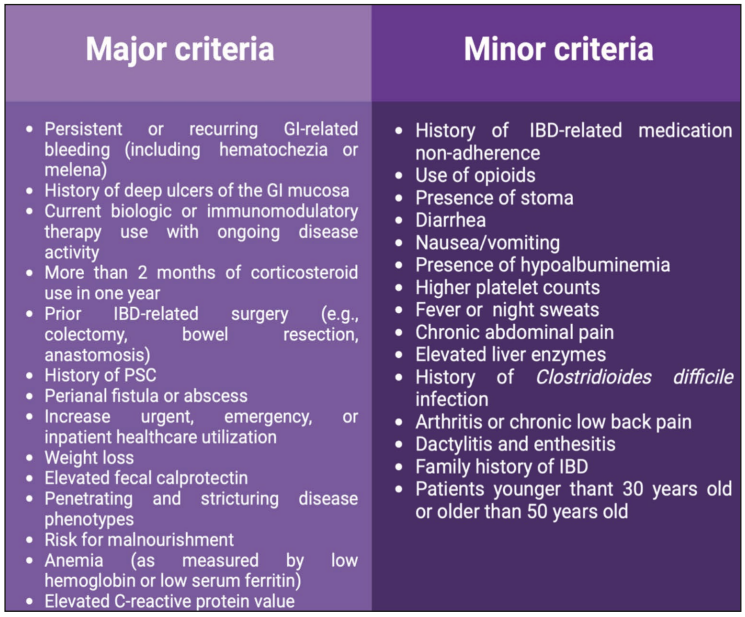

Figure 2 - Major and minor criteria for an appropriate referral of patients with suspected inflammatory bowel diseases between rheumatologist and gastroenterologist. PSC=Primary Sclerosing Cholangitis. Modified from Scott *et al.* (50). Created with BioRender.

Who could benefit from a rheumatologic consultation?

ASAS has developed a set of criteria for diagnosing and classifying peripheral and ax-SpA. Based on the ASAS criteria, the presence of chronic (>3 months) back pain in people under 45 years of age identifies SpA, if sacroiliitis along with at least one typical SpA feature is present [*e.g.*, IBP, arthritis, enthesitis, uveitis, dactylitis, psoriasis, CD/UC, good response to non-steroidal anti-inflammatory drugs (NSAIDs), family history for SpA, HLA-B27, elevated C-reactive protein (CRP)], or if HLA-B27 is present along with at least two other SpA features. Peripheral SpA could be identified in patients with arthritis and enthesitis and/or dactylitis plus one or more other parameters (psoriasis, IBD, previous infection, HLA-B27, uveitis, sacroiliitis on imaging) or two or more other parameters (arthritis, enthesitis, dactylitis, history of IBP, family history of SpA) (51). Peripheral arthritis associated with IBD is categorized into two types. Type 1 affects fewer than five joints and is characterized by acute, self-limiting flares lasting less than ten weeks, often occurring

during IBD activity. Type 2 affects five or more joints and lasts for months and years, independent of IBD flares (52).

The typical symptoms of AS are chronic (at least 3 months) almost daily back pain, often accompanied by morning stiffness. Chronic back pain has the following characteristics: it worsens in the second half of the night and the morning, is relieved by activity and worsened by rest, and is typically improved by NSAIDs (22). To be recognized as a patient with IBP, four of the following five criteria must be met: age at onset <40 years, insidious onset, improvement with exercise, no improvement in back pain at rest, or waking up due to back pain at night (53). The main complaint of axSpA is back pain, but only 5% of patients with chronic back pain can be diagnosed with axSpA (32, 33).

In daily practice, SpA symptoms are not always recognized in patients with IBD. The gastroenterologist should be familiar with the various features of SpA to be able to categorize joint symptoms. According to Zhao *et al*., the average delay to diagnosis in axSpA is 6.7 years (54). As seen for the IBD patients, some clinical red flags can be very useful in clinical practice for an appropriate referral to a rheumatologist: back pain for more than 3 months, recurrent or chronic (more than 3 months) peripheral joint pain or swelling, IBP, finger swelling (*e.g*., dactylitis) ever, heel pain (*e.g*., enthesitis), family history of SpA (48, 50). Carubbi *et al*. schematically analyzed SpA screening tools in patients with IBD and found that their performance in clinical practice is still limited and that it is difficult to differentiate between patients with inflammatory, degenerative (*e.g*., osteoarthritis, degenerative disc disease), or chronic widespread (*e.g.*, fibromyalgia) pain (28). The DETection of Arthritis in Inflammatory Bowel Disease questionnaire is a 6-item questionnaire (*e.g*., *Have you ever had a finger or a toe and/or another joint swollen and painful for no apparent reason? Occasionally, has an entire finger or toe become swollen, making it look like a "sausage"? Have you had pain in your heels? Have you ever had back pain lasting at least 3 months that was not injury-related? Do you have lower back pain in the morning and after resting, which improves with exercise? Do you wake up at night because of low back pain*?) that must be answered with "yes" or "no" and can be given to IBD patients. The combination of at least three positively answered questions results in a probability of SpA of 75% or more (55, 56). Another tool is the 14-question Identification of SpA Questionnaire, in which three positive answers are decisive. It helps to avoid delays in diagnosis, modify the natural history of SpA in IBD, and enable a patient-tailored therapeutic approach with medications that can treat both conditions (57).

A meta-analysis on SpA, which mainly included papers on axSpA, showed a significant difference in diagnostic delay of 2.3 years in women compared to men, despite the same age at onset of symptoms (58). The EMAS study, an online cross-sectional survey of patients with a self-reported diagnosis of axSpA encompassing 13 European countries, shows that in Italy, the average delay in diagnosis is 5.2 years, and a longer diagnostic delay in axSpA is associated with female gender (59). In an observational cross-sectional study, Cumbrera *et al.* showed that women who are diagnosed with axSpA significantly later have a shorter duration of illness and are more likely to consult a general practitioner, osteopath, or physiotherapist before making a definitive diagnosis. Women also have a lower frequency of HLA-B27 positivity, and different disease manifestations (23, 60). As Redeker *et al.* have shown, female gender and HLA-B27 negativity are also associated with a significant delay in the diagnosis of axSpA (61). Poor functional impairment, rapid radiological progression, poor quality of life, and a lower response to treatment are associated with the delay in the diagnosis of SpA (62). Even though female patients have less radiological damage, they have a higher disease burden due to a longer diagnostic delay and lower treatment efficacy, as shown by Rusman *et al.* in their recent review (63). Chimenti *et al.* showed that the longer diagnostic delay in women is due to the following reasons: different pat-

terns or clinical presentations (*e.g.*, women often complain of peripheral manifestations of axSpA, arthritis, and enthesitis, as widespread pain that can be misdiagnosed as fibromyalgia, rather than chronic back pain) and higher prevalence of nr-axSpA. Different disease manifestations make the diagnosis more difficult, leading to an underrepresentation in clinical trials of axSpA. This fact has led to a male bias in the classification and treatment of the disease (11). Some symptoms of SpA, such as low back pain, morning stiffness, and pain-related sleep disturbances, are shared with fibromyalgia. These symptoms are often overlooked in women, leading to a gap in the differential diagnosis of SpA. However, they sometimes coexist with enthesitis and peripheral arthritis, which are sometimes misdiagnosed as fibromyalgia (58). Current objective biomarkers (erythrocyte sedimentation rate, CRP) lack sensitivity and specificity, particularly in distinguishing axSpA from non-specific low back pain (64). Figure 3 summarizes the clinical criteria for an early referral between the gastroenterologist and the rheumatologist (28, 65).

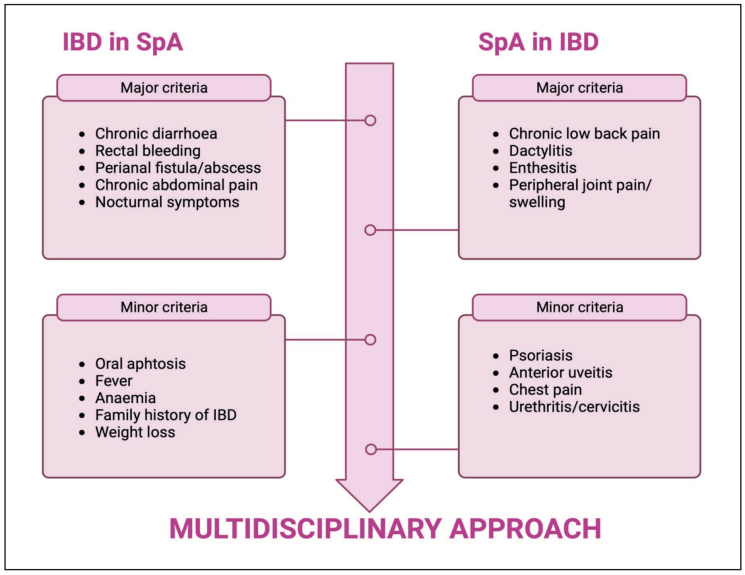

Figure 3 - Clinical criteria for an early referral between the gastroenterologist and the rheumatologist that should lead to a multidisciplinary approach (28, 65). IBD, inflammatory bowel diseases; SpA, spondyloarthritis. Created with BioRender.

MULTIDISCIPLINARY APPROACH

Joint pain is a common symptom and relevant clinical manifestation in IBD patients, and its management requires rheumatological expertise in collaboration with the gastroenterologist, just as the management of IBD symptoms in SpA patients requires the expertise of the gastroenterologist (66). Kumthekar *et al.* showed that IBP and axSpA are often misdiagnosed because of poor knowledge of these diseases (67). As Mathieson *et al.* have shown, only 28% of specialists and about 5% of general practitioners participating in their survey could recognize all eight features of IPB (68). The presence of arthralgias and back pain in IBD patients is associated with lower quality of life, higher fatigue, and more chronic fatigue (69).

Female SpA patients have significantly higher disease activity than male patients in almost all aspects of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), along with greater functional limitation, a higher risk of psychological distress, and a higher prevalence of affective disorders (anxiety and depression) (60). In IBD patients, likewise, female patients are more likely than male patients to report poor quality of life, severe disability, reduced work productivity, and severe depression (24).

Work-related problems are also associated with poorer patient-reported outcomes in SpA patients, both physically (BASDAI) and psychologically (12-item General Health Questionnaire). Psychological distress due to a lack of advancement in careers persists among those receiving disability benefits. Disease duration is also related to work-related problems (70). Rusman *et al.* pointed out that the treatment of axSpA in female patients needs to be improved, as the disease presents differently, radiological progression is slower, and response rates to established therapies are lower (63).

It is undeniable that multidisciplinary teams for SpA-related immune-mediated inflammatory diseases (IMIDs) allow early referral and diagnosis, early detection of con-

comitant IMIDs, and optimization of treatment to improve quality of life. Indeed, a multidisciplinary approach may lead to a more comprehensive assessment of the conditions and a more comprehensive approach to treatment (71). A prospective cohort study has recently shown that clinical outcomes of extramuscular manifestations improved in most patients over 12 months, particularly in patients with recurrent acute anterior uveitis and IBD (72). For a comprehensive overview of the treatment options for both diseases, we recommend a recent publication by Cozzi *et al.* (73) that aims to implement precision medicine for the respective subtypes of SpA and IBD. Currently, the following drugs are approved for both conditions: conventional synthetic disease-modifying antirheumatic drugs, such as methotrexate, sulfasalazine, and azathioprine; tumor necrosis factor inhibitors; interleukin (IL)-12/23 inhibitors or IL-23 inhibitors; and Janus tyrosine kinase inhibitors (73). Establishing a "GastroReumatology" outpatient clinic could be very useful for early-diagnosis patients with these two conditions (74).

CONCLUSIONS

IBD and SpA are chronic inflammatory disorders often occurring in the same patients. Female patients are often misdiagnosed, and this delay in diagnosis is associated with a higher disease burden and a poorer prognosis. It is crucial that gastroenterologists and rheumatologists master all the screening tools that enable early referral, as this means a better prognosis for patients and a reduction in the economic and social burden associated with these diseases. Tailored counseling, particularly for women, addressing their unique needs concerning sexuality, fertility, pregnancy, and breastfeeding, stands as an essential aspect of holistic patient care (75).

Contributions
FZ, CC, designed the manuscript; CC, collected data; CC, FZ, and wrote the manuscript; BB, GL, RR, EVS, revised and approved the final version.

Conflict of interest
FZ, has served as speaker for Werfen, EG Stada Group, Fresenius Kabi, Kedrion, Janssen, Pfizer, Takeda, Unifarco, Malesci, Galapagos; has served as consultant for Galapagos and Takeda. EVS, has served as speaker for Abbvie, AGPharma, Alfasigma, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Unifarco; has served as consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Falk, Fresenius Kabi, Janssen, Merck & Co, Reckitt Benckiser, Regeneron, Sanofi, Shire, ILA, Sofar, Synformulas GmbH, Takeda, Unifarco; has received research support from Reckitt Benckiser, SILA, Sofar, Unifarco. BB, has served as speaker for Abbvie, Agave, Alfasigma, AGpharma, Janssen, MSD, Pfizer, Procise, Sofar, Takeda, Unifarco; has served as consultant for Abbvie and Janssen. RR, consulting and/or speaking fees, Advisory Boards from Abbvie, Novartis, Janssen, Lilly, MSD, Pfizer, and UCB. CC, GL, declare no conflict of interest.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Not applicable.

Funding
None.

Availability of data and materials: data available from the corresponding author upon request.

REFERENCES

1. Gros B, Kaplan GG. Ulcerative colitis in adults: a review. JAMA 2023; 330: 951-65.
2. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, et al. Crohn's disease. Nat Rev Dis Primers 2020; 6: 22.
3. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017; 390: 73-84.
4. Cantoro L, Di Sabatino A, Papi C, Margagnoni G, Ardizzone S, Giuffrida P, et al. The time course of diagnostic delay in inflammatory bowel disease over the last sixty years: an Ital-

ian multicentre study. J Crohns Colitis 2017; 11: 975-80.
5. Cantoro L, Monterubbianesi R, Falasco G, Camastra C, Pantanella P, Allocca M, et al. The earlier you find, the better you treat: red flags for early diagnosis of inflammatory bowel disease. Diagnostics 2023; 13: 3183.
6. Roisinblit KC. Irritable bowel syndrome in women. J Midwifery Womens Health 2013; 58: 15-24.
7. Huang KY, Wang FY, Lv M, Ma XX, Tang XD, Lv L. Irritable bowel syndrome: epidemiology, overlap disorders, pathophysiology and treatment. World J Gastroenterol 2023; 29: 4120-35.
8. Rustøen T, Wahl AK, Hanestad BR, Lerdal A, Paul S, Miaskowski C. Age and the experience of chronic pain. Clin J Pain 2005; 21: 513-23.
9. Aloush V, Ablin JN, Reitblat T, Caspi D, Elkayam O. Fibromyalgia in women with ankylosing spondylitis. Rheumatol Int 2007; 27: 865-8.
10. Barnett R, Gaffney K, Sengupta R. Diagnostic delay in axial spondylarthritis: a lost battle?. Best Pract Res Clin Rheumatol 2023; 37: 101870.
11. Chimenti MS, Alten R, D'Agostino MA, Gremese E, Kiltz U, Lubrano E, et al. Sex-associated and gender-associated differences in the diagnosis and management of axial spondyloarthritis: Addressing the unmet needs of female patients. RMD Open 2021; 7: e001681
12. Wendling D, Hecquet S, Fogel O, Letarouilly JG, Verhoeven F, Pham T, et al. 2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis. Joint Bone Spine 2022; 89: 105344.
13. Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: east meets west. J Gastroenterol Hepatol 2020; 35: 380-9.
14. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015; 12: 720-7.
15. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2021; 18: 56-66.
16. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020; 5: 17-30.
17. Zarco P, González CM, Rodríguez De La Serna A, Peiró E, Mateo I, Linares L, et al. Extraarticular disease in patients with spondyloarthritis. Baseline characteristics of the spondyloarthritis cohort of the AQUILES study. Reumatol Clin 2015; 11: 83-9.
18. Hedin CRH, Vavricka SR, Stagg AJ, Schoepfer A, Raine T, Puig L, et al. The pathogenesis of extraintestinal manifestations: implications for IBD research, diagnosis, and therapy. J Crohns Colitis 2019; 13: 541-54.
19. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018; 16: 343-56.e3.
20. Vavricka SR, Rogler G, Gantenbein C, Spoerri M, Vavricka MP, Navarini AA, et al. Chronological order of appearance of extraintestinal manifestations relative to the time of IBD diagnosis in the Swiss Inflammatory Bowel Disease Cohort. Inflamm Bowel Dis 2015; 21: 1794-800.
21. Varkas G, Ribbens C, Louis E, Van den Bosch F, Lories R, Vermeire S, et al. Expert consensus: practical algorithms for management of inflammatory bowel disease patients presenting with back pain or peripheral arthropathies. Aliment Pharmacol Ther 2019; 50: 1204-13.
22. Navarro-Compán V, Sepriano A, El-Zorkany B, van der Heijde D. Axial spondyloarthritis. Ann Rheum Dis 2021; 80: 1511-21.
23. Lorenzin M, Cozzi G, Scagnellato L, Ortolan A, Vio S, Striani G, et al. Relationship between sex and clinical and imaging features of early axial spondyloarthritis: results from a 48 month follow-up (Italian arm of the SPondyloArthritis Caught Early (SPACE) study). Scand J Rheumatol 2023; 52: 519-29.
24. Goodman WA, Erkkila IP, Pizarro TT. Sex matters: impact on pathogenesis, presentation and treatment of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2020; 17: 740-54.
25. Algaba A, Guerra I, Ricart E, Iglesias E, Mañosa M, Gisbert JP, et al. Extraintestinal manifestations in patients with inflammatory bowel disease: study based on the ENEIDA registry. Dig Dis Sci 2021; 66: 2014-23.
26. Peluso R, Di Minno MND, Iervolino S, Manguso F, Tramontano G, Ambrosino P, et al. Enteropathic spondyloarthritis: from diagnosis to treatment. Clin Dev Immunol 2013; 2013: 631408.
27. Zioga N, Kogias D, Lampropoulou V, Kafalis N, Papagoras C. Inflammatory bowel disease-related spondyloarthritis: the last unexplored territory of rheumatology. Mediterr J Rheumatol 2022; 33: 126-36.
28. Carubbi F, Alunno A, Viscido A, Baraliakos X, Mariani FM, Di Ruscio E, et al. SpA plus IBD or IBD plus SpA: does commutative property apply?. Autoimmun Rev 2023; 22: 103443.
29. Harbord M, Annese V, Vavricka SR, Allez M, Acosta MB de, Boberg KM, et al. The first european evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016; 10: 239-54.
30. 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.
31. Ono K, Kishimoto M, Deshpande GA, Fukui S, Kawaai S, Sawada H, et al. Clinical characteristics of patients with spondyloarthritis and inflammatory bowel disease versus inflammatory bowel disease-related arthritis. Rheumatol Int 2022; 42: 1751-66.
32. Maguire S, Wilson F, Gallagher P, O'Shea FD. Worse scores but similar patterns of disease activity: interpreting outcomes in women with axial spondyloarthropathy. Scand J Rheumatol 2023; 52: 142-9.
33. Wendling D, Guillot X, Prati C, Miceli-Richard C, Molto A, Lories R, et al. Effect of gut involvement in patients with high probability of early spondyloarthritis: data from the DESIR cohort. J Rheumatol 2020; 47: 349-53.
34. Felice C, Dal Buono A, Gabbiadini R, Rattazzi M, Armuzzi A. Cytokines in spondyloarthritis and inflammatory bowel diseases: from pathogenesis to therapeutic implications. Int J Mol Sci 2023; 24: 3957.
35. Shen YH, Zhu H, Zhou L, Zheng YQ, Zhang Z, Xie Y, et al. In inflammatory bowel disease and extraintestinal manifestations: what role does microbiome play?. Engineered Regeneration 2023; 4: 337-48.
36. Salmi M, Jalkanen S. Human leukocyte subpopulations from inflamed gut bind to joint vasculature using distinct sets of adhesion molecules. J Immunol 2001; 166: 4650-7.
37. Arvikar SL, Fisher MC. Inflammatory bowel disease associated arthropathy. Curr Rev Musculoskelet Med 2011; 4: 123-31.
38. May E, Märker-Hermann E, Wittig BM, Zeitz M, Büschenfelde KMZ, Duchmann R. Identical T-cell expansions in the colon mucosa and the synovium of a patient with enterogenic spondyloarthropathy. Gastroenterology 2000; 119: 1745-55.
39. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 2019; 13: 144-64.
40. 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.
41. Schoepfer AM, Dehlavi MA, Fournier N, Safroneeva E, Straumann A, Pittet V, et al. Diagnostic delay in crohn's disease is associated with a complicated disease course and increased operation rate. Am J Gastroenterol 2013; 108: 1744-53.
42. Danese S, Fiorino G, Mary JY, Lakatos PL, D'Haens G, Moja L, et al. Development of red flags index for early referral of adults with symptoms and signs suggestive of Crohn's disease: an IOIBD initiative. J Crohns Colitis 2015; 9: 601-6.
43. Nahon S, Lahmek P, Lesgourgues B, Poupardin C, Chaussade S, Peyrin-Biroulet L, et al. Diagnostic delay in a French cohort of Crohn's disease patients. J Crohns Colitis 2014; 8: 964-9.
44. Sempere L, Bernabeu P, Cameo J, Gutiérrez A, García MG, García MF, et al. Gender biases and diagnostic delay in inflammatory bowel disease: multicenter observational study. Inflamm Bowel Dis 2023; 29: 1886-94.
45. Fauny M, D'Amico F, Bonovas S, Netter P, Danese S, Loeuille D, et al. Faecal calprotectin for the diagnosis of bowel inflammation in patients with rheumatological diseases: a systematic review. J Crohns Colitis 2020; 14: 688-93.
46. Ananthakrishnan AN, Adler J, Chachu KA, Nguyen NH, Siddique SM, Weiss JM, et al. AGA Clinical practice guideline on the role of biomarkers for the management of crohn's disease. Gastroenterology 2023; 165: 1367-99.
47. Feng HY, Chan CH, Chu YC, Qu XM, Wang YH, Wei JCC. Patients with ankylosing spondylitis have high risk of irritable bowel syndrome: a long-term nationwide population-based cohort study. Postgrad Med 2022; 134: 290-6.
48. Felice C, Leccese P, Scudeller L, Lubrano E, Cantini F, Castiglione F, et al. Red flags for appropriate referral to the gastroenterologist and the rheumatologist of patients with inflammatory bowel disease and spondyloarthritis. Clin Exp Immunol 2019; 196: 123-38.
49. Fiorino G, Bonovas S, Gilardi D, Di Sabatino A, Allocca M, Furfaro F, et al. Validation of the red flags index for early diagnosis of crohn's disease: a prospective observational IG-IBD study among general practitioners. J Crohns Colitis 2021; 14: 1777-9.
50. Scott FI, Ehrlich O, Wood D, Viator C, Rains C, DiMartino L, et al. Creation of an inflammatory bowel disease referral pathway for identifying patients who would benefit from inflammatory bowel disease specialist consultation. Inflamm Bowel Dis 2023; 29: 1177-90.
51. Rudwaleit M, Van Der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011; 70: 25-31.
52. Salvarani C, Fries W. Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease. World J Gastroenterol 2009; 15: 2449-55.
53. Sieper J, Van Der Heijde D, Landewé R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient

exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009; 68: 784-8.
54. Zhao SS, Pittam B, Harrison NL, Ahmed AE, Goodson NJ, Hughes DM. Diagnostic delay in axial spondyloarthritis: A SYSTEMATIC REVIEW AND META-ANALYSIS. Rheumatology 2021; 60: 1620-8.
55. 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.
56. Benfaremo D, Luchetti MM, Di Carlo M, Salaffi F, Gabrielli A, Benedetti A, et al. Multicenter validation of the DETAIL questionnaire for the screening of spondyloarthritis in patients with inflammatory bowel diseases. J Rheumatol 2021; 48: 179-87.
57. Variola A, Zanolin ME, Cipriano G, Macchioni P, Martinis F, Pasetti A, et al. The IBIS-Q [IBd Identification of Spondyloarthritis Questionnaire]: a novel tool to detect both axial and peripheral arthritis in inflammatory bowel disease patients. J Crohns Colitis 2020; 14: 1680-6.
58. Jovaní V, Blasco-Blasco M, Ruiz-Cantero MT, Pascual E. Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and metaanalysis. J Rheumatol 2017; 44: 174-83.
59. Garrido-Cumbrera M, Navarro-Compán V, Bundy C, Mahapatra R, Makri S, Correa-Fernández J, et al. Identifying parameters associated with delayed diagnosis in axial spondyloarthritis: data from the European map of axial spondyloarthritis. Rheumatology 2022; 61: 705-12.
60. Garrido-Cumbrera M, Poddubnyy D, Gossec L, Mahapatra R, Bundy C, Makri S, et al. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). Clin Rheumatol 2021; 40: 2753-61.
61. Redeker I, Callhoff J, Hoffmann F, Haibel H, Sieper J, Zink A, et al. Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. Rheumatology 2019; 58: 1634-8.
62. Lee SC, Yang CH, Tsai YC, Yu KH. The effect of uveitis and undiagnosed spondyloarthritis: a systematic review and meta-analysis. Sci Rep 2023; 13: 14779.
63. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018; 20: 35.
64. Reveille JD. Biomarkers in axial spondyloarthritis and low back pain: a comprehensive review. Clin Rheumatol 2022; 41: 617-34.
65. Sanz Sanz J, Juanola Roura X, Seoane-Mato D, Montoro M, Gomollón F. Screening of inflammatory bowel disease and spondyloarthritis for referring patients between rheumatology and gastroenterology. Reumatol Clin (Engl Ed) 2018; 14: 68-74.
66. 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.
67. Kumthekar A, Bittar M, Dubreuil M. Educational needs and challenges in axial spondyloarthritis. Curr Opin Rheumatol 2021; 33: 313-8.
68. Mathieson HR, Merashli M, Gaffney K, Marzo-Ortega H. Poor awareness of inflammatory back pain and axial spondyloarthritis among secondary care specialists. Clin Rheumatol 2016; 35: 2627-8.
69. Ossum AM, Palm Ø, Cvancarova M, Bernklev T, Jahnsen J, Moum B, et al. The impact of spondyloarthritis and joint symptoms on health-related quality of life and fatigue in IBD patients. Results from a population-based inception cohort (20-year follow-up in the Ibsen Study). Inflamm Bowel Dis 2020; 26: 114-24.
70. Inman RD, Garrido-Cumbrera M, Chan J, Cohen M, de Brum-Fernandes AJ, Gerhart W, et al. Work-related issues and physical and psychological burden in canadian patients with axial spondyloarthritis: results from the international map of axial spondyloarthritis. J Rheumatol 2023; 50: 625-33.
71. Rizzello F, Olivieri I, Armuzzi A, Ayala F, Bettoli V, Bianchi L, et al. Multidisciplinary management of spondyloarthritis-related immune-mediated inflammatory disease. Adv Ther 2018; 35: 545-62.
72. Dos Reis Annunciato D, Oliveira TL, Magalhães VO, de Medeiros Pinheiro M. Extra-musculoskeletal manifestations driving the therapeutic decision-making in patients with spondyloarthritis: a 12-month follow-up prospective cohort study. Adv Rheumatol 2023; 63: 44.
73. Cozzi G, Scagnellato L, Lorenzin M, Savarino E, Zingone F, Ometto F, et al. Spondyloarthritis with inflammatory bowel disease: the latest on biologic and targeted therapies. Nat Rev Rheumatol 2023; 19: 503-18.
74. Lorenzetti R, Scolieri P, Guarini A, de Marinis F, Zullo A, Hassan C, et al. Integrated gastroenterology and rheumatology ambulatory: an innovative approach for enteropathic spondyloarthritis early diagnosis. Ann Ist Super Sanita 2019; 55: 246-8.
75. Torres J, Chaparro M, Julsgaard M, Katsanos K, Zelinkova Z, Agrawal M, et al. European crohn's and colitis guidelines on sexuality, fertility, pregnancy, and lactation. J Crohns Colitis 2023; 17: 1-27.