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Red flags for appropriate referral to the gastroenterologist and the rheumatologist of patients with inflammatory bowel disease and spondyloarthritis

C. Felice,* P. Leccese,† L. Scudeller,‡ E. Lubrano,§ F. Cantini,¶ F. Castiglione,** P. Gionchetti,†† A. Orlando,‡‡ C. Salvarani,§§ R. Scarpa,¶¶ M. Vecchi,*** I. Olivieri†[1] and A. Armuzzi *[1] and on behalf of the Italian SpA-IBD Expert Panel Group

*IBD Unit, Presidio Columbus, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore, Rome, Italy, †Rheumatology Institute of Lucania (IRel) and the Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, ‡Clinical Epidemiology Unit, IRCCS Policlinico San Matteo Foundation, Pavia, Italy, §Academic Rheumatology Unit, Dipartimento di Medicina e Scienze della Salute 'Vincenzo Tiberio', Università degli Studi del Molise, Campobasso, Italy, ¶Division of Rheumatology, Hospital of Prato, Italy, **Gastroenterology Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy, ††IBD Unit, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Italy, ‡‡IBD Unit, A.O. Ospedali Riuniti 'Villa Sofia-Cervello', Palermo, Italy, §§Azienda USL - IRCCS di Reggio Emilia e, Università di Modena e Reggio Emilia, Italy, ¶¶Rheumatology Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy, and ***Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Pathophysiology and Organ Transplantation, University of Milan, Italy

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Correspondence: A. Armuzzi, IBD Unit, Presidio Columbus, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica del Sacro Cuore, Via Moscati 31-33, 00168, Rome, Italy.
E-mail: alearmuzzi@yahoo.com

[1]Deceased.

Summary

Collaboration between gastroenterologists and rheumatologists is recommended for the correct management of patients with associated spondyloarthritis (SpA) and inflammatory bowel disease (IBD). We aimed to establish the appropriateness of several red flags for a prompt specialist referral. A systematic review of the literature was performed using the GRADE method to describe the prevalence of co-existing IBD-SpA and the diagnostic accuracy of red flags proposed by a steering committee. Then, a consensus among expert gastroenterologists and rheumatologists (10 in the steering committee and 13 in the expert panel) was obtained using the RAND method to confirm the appropriateness of each red flag as 'major' (one sufficient for patient referral) or 'minor' (at least three needed for patient referral) criteria for specialist referral. The review of the literature confirmed the high prevalence of co-existing IBD-SpA. Positive and negative predictive values of red flags were not calculated, given the lack of available data. A consensus among gastroenterology and rheumatology specialists was used to confirm the appropriateness of each red flag. Major criteria to refer patients with SpA to the gastroenterologist included: rectal bleeding, chronic abdominal pain, perianal fistula or abscess, chronic diarrhoea and nocturnal symptoms. Major criteria to refer patients with IBD to the rheumatologist included: chronic low back pain, dactylitis, enthesitis and pain/swelling of peripheral joints. Several major and minor red flags have been identified for the diagnosis of co-existing IBD-SpA. The use of red flags in routine clinical practice may avoid diagnostic delay and reduce clinic overload.

Keywords: inflammatory bowel disease, red flag, spondyloarthritis

Introduction

Inflammatory bowel diseases (IBD, including Crohn's disease (CD) and ulcerative colitis (UC) and spondyloarthritis (SpA), are chronic disorders which may co-exist in the same subject, worsening the disability and the quality of life of the patient and making the clinical management of the diseases more complicated. It is noteworthy that SpA is reported in the literature as the most common extra-intestinal manifestation in IBD patients [1–5]. However, this still represents an underestimated clinical problem, as demonstrated by Stolwijk *et al.* in a Dutch study: among 350 IBD patients, 129 (39·6%) reported articular symptoms suggestive of SpA, but only half of them were referred to a rheumatologist [5]. A prompt and correct diagnosis of these disorders may have a significant impact on their therapeutic management, influencing the type and duration of therapies [6,7] and possibly preventing the complications related to progressive and potentially irreversible intestinal and articular tissue damage. Conversely, symptoms not specifically related to inflammatory conditions may induce inappropriate referral, causing clinic overload. Therefore, direct collaboration between gastroenterologists and rheumatologists is fundamental, and may benefit from the identification of 'red flags' (disease-specific signs and symptoms) for easier and more appropriate patient referral.

Recently, several red flags have been proposed to facilitate early referral of patients with Crohn's disease from primary to specialist care and thus avoid diagnostic delay [8]. Moreover, a six-item questionnaire (DETAIL) has been developed to screen patients with IBD for the diagnosis of SpA, but it needs to be validated in larger cohorts of patients [9].

This study aimed to obtain a consensus among gastroenterology and rheumatology specialists on the adequateness of several 'red flags' for a correct referral of patients with IBD and SpA from the gastroenterologist to the rheumatologist (and vice versa).

Methods

The entire process was developed throughout several meetings, from December 2016 to October 2017. 'Red flags' were defined as signs or symptoms which may alert to a possible diagnosis of IBD in a patient with axial or peripheral SpA, or (analogously) may alert to a possible diagnosis of axial or peripheral SpA in a patient with IBD, allowing a prompt referral to the relevant clinical specialist (Table 1).

Project management

The steering committee was the same as previous projects already published concerning the management of this particular clinical setting [6,7] and included 10 Italian rheumatologists and gastroenterologists with definitive expertise in the field of SpA and IBD identified according to their publication record, participation in national meetings and clinical trials and/or senior academic rank. Two clinical fellows (C.F. and P.L.) performed the systematic review of the literature. The expert panel was composed of 13 gastroenterologists and rheumatologists from different

Table 1. Definition of gastrointestinal and rheumatological red flags selected by the Steering Committee

'Red flag': sign or symptom suggestive of a specific disease	
Red flags for IBD	Red flags for SpA
Chronic diarrhoea (change in the bowel habit with loose stools and/or increase of bowel movements per day lasting >4 weeks)	Chronic low back pain (>3 months)
Chronic abdominal pain (>3 months) [8]	Family history of SpA (presence in first-degree or second-degree relatives of any of the following: AS, psoriasis, acute uveitis, reactive arthritis, IBD [73]
Rectal bleeding (not from haemorrhoids)	Peripheral joint pain*/swelling
Weight loss (>5% in the last 3 months [8], involuntarily)	Dactylitis (past or present, diagnosed by a doctor) [73]
Fever (no otherwise explained and associated to raised inflammatory markers)	Enthesitis (heel enthesitis: past or present spontaneous pain or tenderness at examination at the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus) [73]
Family history of IBD	Psoriasis (past or present, diagnosed by a doctor) [73]
Anaemia (no otherwise explained)	Anterior uveitis (past or present, and confirmed by an ophthalmologist) [73]
Perianal fistula or abscess (past or current)	Urethritis/cervicitis (within 1 month before the onset of arthritis/enthesitis/dactylitis) [73]
Nocturnal symptoms (diarrhoea or abdominal pain)	Chest pain
Oral aphtosis (recurrent)	

IBD = inflammatory bowel disease; SpA = spondyloarthritis; AS = ankylosing spondylitis.

*Recurrent or lasting >3 months.

Table 2. GRADE model for diagnostic tests used for the literature search

Population	Rheumatological patient	Gastroenterological patient
	• AxSpA • pSpA	• IBD • UC • CD
Diagnostic test ('red flag')	Gastrointestinal signs or symptoms • Family history of IBD • Rectal bleeding • Weight loss • Chronic abdominal pain • Anaemia • Perianal fistula or abscess • Fever • Chronic diarrhoea • Nocturnal symptoms • Oral apthosis	Rheumatological signs or symptoms • Family history of SpA • Chronic low back pain • Psoriasis • Dactylitis • Heel/knee enthesitis • Anterior uveitis • Urethritis/cervicitis • Peripheral joint swelling/pain • Chest pain
Control (absence of 'red flag')	Absence of gastrointestinal symptoms	Absence of rheumatological symptoms
Outcome	Diagnosis of gastrointestinal disease • IBD • UC • CD	Diagnosis of rheumatological disease: • AxSpA • pSpA

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; SpA = spondyloarthritis; AxSpA = axial spondyloarthritis; pSpA = peripheral spondyloarthritis.

Italian regions (Supporting information, Appendix 1). A clinical epidemiologist with expertise in the GRADE framework and consensus methods was also involved (L.S.), as well as an experienced medical librarian.

Systematic literature review

The GRADE framework for diagnostic tests was used to formulate the search questions (Table 2), with the definition of patients, diagnostic test (in our case, 'red flag'), comparison (in our case, the absence of 'red flag') and outcomes of interest [10].

To estimate the positive and negative predictive value (post-test probability) of each red flag, information about the prevalence of the disease (pre-test probability) and test accuracy (sensitivity and specificity) would be needed. Therefore, different systematic reviews were performed to address the following issues:

- the prevalence of SpA in patients with an established diagnosis of IBD;
- the prevalence of IBD in patients with an established diagnosis of SpA;
- the diagnostic accuracy of rheumatological red flags in IBD patients; and
- the diagnostic accuracy of gastrointestinal red flags in SpA patients.

PubMed and EMBASE were interrogated for the search, without initial date limit, until January 2017. Only English papers were included, and abstracts without full text were excluded. Details of search terms for prevalence data are available in the Supporting information.

Statistical analyses

Abstract and full texts were assessed for eligibility, and data were extracted by the clinical fellows (C.F. and P.L.) in two dedicated spreadsheets (one for SpA and one for IBD), in duplicate. The *metan* suite of commands in STATA version 14 was used for data synthesis, using random effect models. Heterogeneity was assessed by means of the I^2 statistic. The sources of heterogeneity that were explored were specific diagnosis (AxSpA/pSpA, CD/UC/IBD) in all population/outcome combinations (i.e. all possible scenarios) and (for diagnostic accuracy) in each individual red flag.

To obtain a rough estimate of the positive and negative predictive value of each red flag for the population/outcome combination of interest, the Bayes formula was applied, informed with estimates obtained in the meta-analysis.

RAND method

Given the results of the systematic review (see Results), the RAND method [11] was used to define the appropriateness of patient referral from the gastroenterologist to the rheumatologist and vice versa, when specific signs or symptoms (red flags) suggest co-existing IBD-SpA in a number of clinical scenarios.

Expert opinion

Based on the results of the systematic review of the literature and their personal opinion, the gastroenterology

and rheumatology specialists participated in two rounds of an online survey (the first in June 2017 and the second in August 2017) to define the appropriateness of gastroenterology or rheumatology referral for each red flag. A procedure (in this case: referral to a clinical specialist) should be considered appropriate when 'the expected health benefit […] exceeds the expected negative consequences […] by a sufficiently wide margin that the procedure is worth doing, exclusive of cost' [11–13].

A nine-point scale was used to quantify appropriateness of referral, considering '1' as absolutely inappropriate, '5' as uncertain and '9' as absolutely appropriate. The median score was used to classify appropriateness (1–3 inappropriate, 4–6 probably appropriate, 7–9 always appropriate), and the 30–70th interpercentile range corrected for asymmetry (IPRAS) was used to assess disagreement. After viewing the results of the first round, in which their responses were highlighted, panel members were asked to review their choices in the second round.

Final consensus

The final meeting was held on 10 October 2017 in Rome, Italy. The goal was to reach consensus on the final classification of each red flag as 'major' (1 red flag sufficient for patient referral) or 'minor' (>1 red flag needed for patient referral) and to establish how many minor red flags are required to justify patient referral in both gastroenterological and rheumatological settings. All questions were formulated as: 'Do you agree to consider this red flag as "major" criteria for referral in this scenario?' or 'do you agree that a minimum of three *minor* red flags are needed for referral?', allowing 'yes', 'no' or 'no opinion' as responses. All votes were expressed electronically and anonymously. Consensus was defined as >70% of the panel agreeing for 'yes' with <15% of the panel responding 'no'.

Results

Systematic review

A total of 28 384 non-duplicate records were screened at the abstract level: 939 for the prevalence of co-existing IBD-SpA (Fig. 1); 15 954 for the diagnostic accuracy of gastrointestinal red flags; and 11 491 for rheumatological red flags (Supporting information, Figs. S1 and S2). Then, 378 full texts were assessed for eligibility and, finally, 78 papers were included in the qualitative and quantitative analysis: 67 for the analysis of the prevalence of co-existing IBD-SpA [2–4,14–77] (Tables 3 and 4) and only 11 for the diagnostic accuracy of red flags [8,78–87].

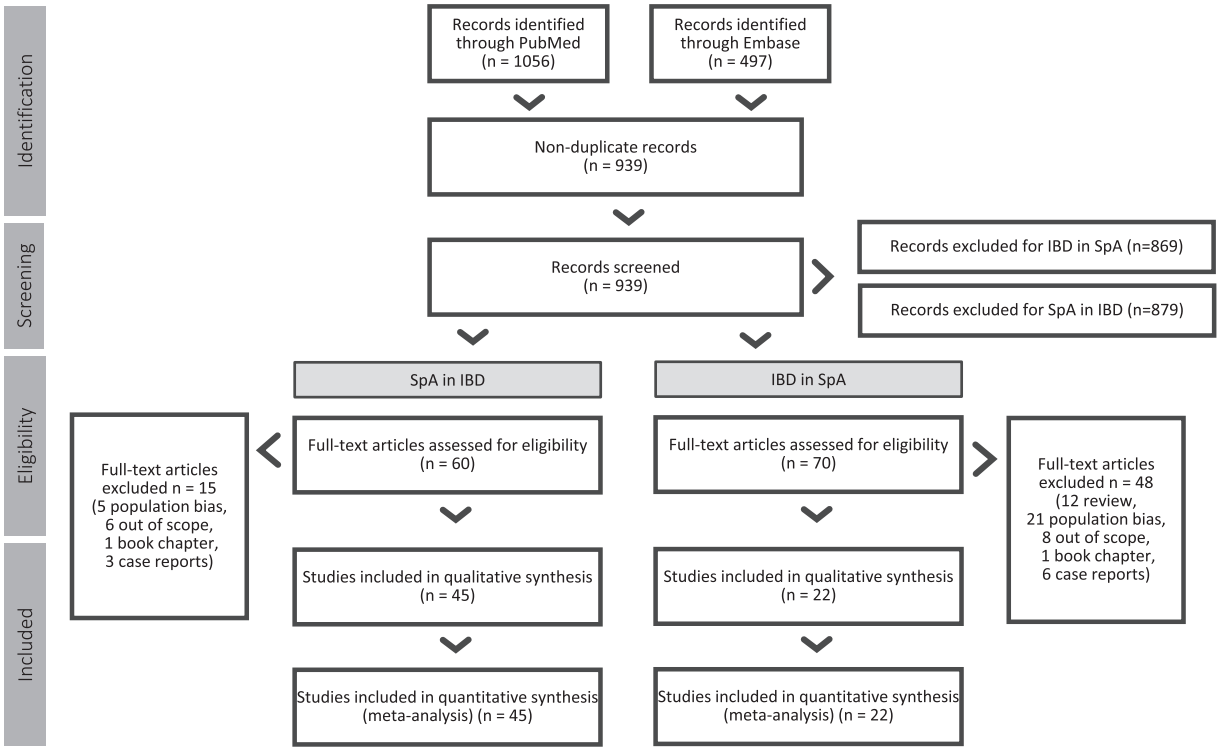

Fig. 1. Flowchart of study selection for prevalence of co-existing inflammatory bowel diseases (IBD) and spondyloarthritis (SpA) ('SpA in IBD': prevalence of SpA among patients with a diagnosis of IBD; 'IBD in SpA': prevalence of IBD in patients with a diagnosis of SpA).

Table 3. Characteristics of studies included in the analysis of prevalence of SpA in IBD patients

Author (year)	Study design	Country	Population (*n* diagnosis)	SpA (*n* diagnosis)	Prevalence SpA (%)
Al-Jarallah (2013) [14]	Prospective cross-sectional	Kuwait	130 IBD (45 UC, 85 CD)	41 PSpA	31·5
				15 AxSpA	11·5
				4 SA	3·1
				7 Entesopathy	5·4
				2 Dactylitis	1·5
Bandinelli (2014) [15]	Prospective cohort	Italy	81 IBD (26 UC, 55 CD)	22 Radiological SA	27·1
Bandyopadhyay (2015) [16]	Prospective cross-sectional	India	120 IBD (58 UC, 62 CD)	AS	18
				PA	23
Bardazzi (1997) [17]	Prospective cross-sectional	Italy	68 UC	4 AS	5·8
				9 SA	13·2
				6 unclassified SpA	8·8
Barreiro-De Acosta (2007) [18]	Prospective cross-sectional	Spain	173 CD	31 PA	17·9
				12 SA	6·9
				4 AS	2·3
Bernstein (2001) [19]	Population-based registry	Canada	4454 IBD	AS	0·8 (female) 2·1 (male)
Beslek (2009) [20]	Prospective cross-sectional	Turkey	122 IBD (94 UC, 28 CD)	35 SpA	28·7
				10 AS	8·2
Bhat (2009) [21]	Registry	USA/Canada	1489 IBD	PA	7
				SA	4
				AS	2
Bruining (2008) [22]	Retrospective	USA	357 CD	8 Radiological SA	2·2
Christodoulou (2002) [23]	Retrospective	Greece	215 UC	9 SA	4·2
				5 oligo-PA	2·3
				18 poly-PA	8·3
			37 CD	6 SA	16·2
				2 oligo-PA	5·4
				3 poly-PA	8·1
Dekker-Saeys (1978) [25]	Prospective cross-sectional	The Netherlands	109 IBD	4 AS	3·7
				PA	12·8
				Radiological SA	10·1
D'Incà (2009) [24]	Prospective cohort	Italy	385 UC	8 SA	2·1
				4 AS	1
				8 Oligo-PA	2·1
				7 Poly-PA	1·8
			266 CD	15 SA	5·6
				5 AS	1·9
				2 Oligo-PA	0·7
				7 Poly-PA	2·6
Van Erp (2016) [4]	Prospective cohort	The Netherlands	510 IBD	155 SpA	30·4
				Enthesitis	0·7
				Dactylitis	0·7
Hyla (1976) [26]	Prospective cross-sectional	USA	89 IBD	11 Radiological SA	12·4
				4 AS	4·5
Jalan (1970) [27]	Retrospective	Scotland	399 UC	17 AS	4·2
				27 Arthropathy	6·8
				20 Dactylitis	5
Karreman (2016) [28]	Meta-analysis	NA	IBD	SpA	13
				PA	13
				SA	10
				AS	3
				Enthesitis	1
				Dactylitis	6

(Continued)

Table 3. (Continued)

Author (year)	Study design	Country	Population (***n*** diagnosis)	SpA (***n*** diagnosis)	Prevalence SpA (%)
Kochhar (1991) [29]	Prospective cross-sectional	India	150 UC	16 SA	10·7
				21 PA	14
Lanna (2008) [30]	Prospective cross-sectional	Brasil	130 IBD	8 AS	6·2
				7 Enthesitis	5·4
				12 Radiological SA	9·2
				21 PA	16·2
			59 UC	AS	0
				2 Enthesitis	3·4
				Radiological SA	3·4
				PA	11·9
			71 CD	AS	11·3
				5 Enthesitis	7
				Radiological SA	14·1
				PA	19·7
Leclerc-Jacob (2014) [31]	Retrospective	France	186 IBD	31 Radiological SA	16·7
Liu (2016) [32]	Retrospective	China	195 CD	8 AS	4·12
McEniff (1994) [33]	Prospective case series	USA	65 IBD	21 Radiological SA	32
Mocelin (2015) [34]	Retrospective	Brasil	100 CD	6 SpA	6
Modena (1988) [35]	Prospective case series	Italy	51 CD	6 AS	11·7
				8 oligo-PA	15·7
				2 poly-PA	3·9
				6 Radiological SA	11·7
Münch (1986) [36]	Prospective cross-sectional	Germany	167 CD	73 SpA	44
				15 AS	9
				24 SA	14
				23 PA	14
				11 SA + arthritis	7
Orchard (2008) [37]	Prospective case series	UK	44 CD	17 Radiological SA	39
Palm (2002) [38]	Population-based cohort	Norway	521 IBD	15 AS	3·7
				2 Dactylitis	
				1 Enthesitis	
				SpA	22
				Radiological SA	2
Paparo (2012) [39]	Retrospective	Italy	221 CD	53 Radiological SA	24
Peeters (2004) [40]	Prospective cross-sectional	Belgium	102 CD	23 Radiological SA	23
				9 AS	8·8
				17 PA	16·6
				11 Enthesopathy	10·4
Peeters (2008) [41]	Prospective cross-sectional	Belgium	244 CD	65 Radiological SA	27
				16 AS	6·5
Pezerović (2013) [42]	Retrospective population-based	Croatia	150 IBD	32 PA	21·3
				6 SA	4
				8 AS	5·3
			119 UC	24 PA	20·2
				3 SA	2·5
				4 AS	3·4
			31 CD	8 PA	25·8
				3 SA	9·7
				4 AS	12·9
Pokharna (2004) [43]	Prospective cross-sectional	India	46 UC	1 PA	2

(Continued)

Table 3. (Continued)

Author (year)	Study design	Country	Population (*n* diagnosis)	SpA (*n* diagnosis)	Prevalence SpA (%)
Queiro (2000) [44]	Prospective cross-sectional	Spain	62 IBD	15 Radiological SA	24
				19 PA	30
				2 AS	3
Rodriguez (2008) [45]	Prospective cross-sectional	Puerto Rico	100 IBD	42 SpA	42
				2 AS	2
				13 SA	13
				5 PA	5
				3 Dactylitis	3
				2 Enthesitis	2
Salvarani (2001) [2]	Population-based inception cohort	Italy, the Netherlands	160 IBD	29 SpA	18·1
				5 AS	3·1
				23 Unclassified SpA	14·4
Scarpa (1992) [46]	Prospective cross-sectional	Italy	79 UC	20 AS	25·3
				15 PA	19
				14 Unclassified SpA	17·7
Scott (1990) [47]	Prospective cross-sectional	USA	86 CD	25 Radiological SA	29
Sofia (2014) [49]	Retrospective	USA	513 Caucasian UC	10 AS/SA	1·6
			28 African American UC	2 AS/SA	7·1
			1127 Caucasian CD	2.9 AS/SA	2·9
			108 African American CD	3 AS/SA	2·8
Steer (2003) [50]	Prospective cross-sectional	UK	134 CD	31 Radiological SA	23
Suh (1998) [51]	Retrospective	Korea	129 IBD	20 PA	15
				Radiological SA	6·2
				AS	1·6
			77 UC	15 PA	19·6
			52 CD	5 PA	9·6
Sung (1994) [52]	Retrospective	China	15 CD	2 AS	13·3
				1 SA	6·6
				1 Colitic arthritis	6·6
Turkcapar (2006) [3]	Prospective cross-sectional	Turkey	162 IBD	74 SpA	45·7
				16 AS	9·9
				24 PA	14·8
				81 Enthesitis	50
				74 Bilateral SA	45·7
				22 Radiological SA	13·6
			84 UC	36 SpA	42·8
				7 AS	8·3
				12 PA	14·3
				39 Enthesitis	46·4
				36 Bilateral SA	42·8
				12 Radiological SA	14·3
			78 CD	38 SpA	48·7
				9 AS	11·5
				12 PA	15·4
				42 Enthesitis	53·8
				38 Bilateral SA	48·7
				10 Radiological SA	12·8
Vavricka (2011) [53]	Prospective cohort	Swiss	950 IBD	272 Arthritis	28·6
				39 AS	4·1
			370 UC	79 Arthritis	21·3
				6 AS	1·6
			580 CD	193 Arthritis	33·3
				33 AS	5·7

(Continued)

Table 3. (Continued)

Author (year)	Study design	Country	Population (*n* diagnosis)	SpA (*n* diagnosis)	Prevalence SpA (%)
Vavricka (2015) [54]	Registry	Swiss	1249 IBD	60 AS/SA	16·4
				256 Arthritis	70
			483 UC	14 AS/SA	13·4
				62 Arthritis	59·1
			735 CD	45 AS/SA	18·2
				184 Arthritis	74·2
de Vlam (2000) [48]	Prospective cross-sectional		103 IBD	10 AS	10
				10 Synovitis	10
				7 Enthesopathy	7
				33 SA	32
				36 SpA	35
			25 UC	3 AS	12
				3 Synovitis	12
				2 Enthesopathy	4
				6 SA	24
				11 SpA	44
			78 CD	7 AS	9
				7 Synovitis	9
				5 Enthesopathy	8
				27 SA	35
				25 SpA	32
Yi (2012) [55]	Retrospective	China	153 CD	7 Arthritis	4·6
				1 AS	0·65

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; SpA = spondyloarthritis; AxSpA = axial spondyloarthritis; pSpA = peripheral spondyloarthritis; PA = peripheral arthritis; AS = ankylosing spondylitis; SA = sacroiliitis.

Results of this exercise indicated high heterogeneity of prevalence estimates across studies and clinical scenarios (I^2 statistics: 90·3% for prevalence of IBD in AxSpA, 89·1% in pSpA, 96·3% for SpA in CD, 94·7% in UC, 98·1% in IBD, all $P < 0·001$) and low reliability in the estimates of accuracy due to poor quality of evidence. Therefore, the results were not pooled into a summary estimate but used only in a qualitative manner.

There were no studies specifically focused on the diagnostic accuracy of gastroenterological red flags in rheumatological patients, and vice versa. Therefore, the review and the subsequent data analysis included the sensitivity and specificity of red flags in the general population as the best surrogate. For some red flags, there were no specific data on diagnostic accuracy. Considering the impossibility to pool results, and to obtain a reliable summary estimate of the prevalence of co-existing IBD-SpA and diagnostic accuracy of individual red flags, positive and negative predictive values were not calculated.

RAND online surveys

The response rate to the online survey was 100% in both rounds. Nno disagreement was reported after the second round, and all red flags were judged as 'absolutely appropriate' or 'probably appropriate'. Moreover, there was a general overlap between rheumatological (axial and peripheral SpA) and gastrointestinal (IBD, UC and CD) scenarios.

Based on the results of the online survey, red flags were categorized into two possible clinical scenarios: gastrointestinal or rheumatological signs or symptoms in patients with SpA and IBD, respectively. In fact, a more accurate diagnosis (axial or peripheral SpA and CD or UC) is the result of the process guided by the specialist after patient referral and, therefore, was considered out of the scope of this paper.

Final consensus

A total of 22 specialists participated in this final session of the consensus (attendance rate 92%).

The participants were called to vote on the appropriateness of each red flag to confirm the classification as minor or major criteria. Major criteria for the referral of a patient with SpA to the gastroenterologist included: rectal bleeding, chronic abdominal pain, perianal fistula or abscess, chronic diarrhoea and nocturnal symptoms. Major criteria for the referral of a patient with IBD to the rheumatologist included: chronic low back pain, dactylitis, enthesitis and pain/swelling of peripheral joints. All remaining red flags were confirmed to be minor criteria (Table 5). Urethritis/cervicitis was removed from the list of red flags due to its inclusion in other three major criteria (arthritis/enthesitis/dactylitis) [86].

Table 4. Characteristics of studies included in the analysis of prevalence of IBD in SpA patients

Author (year)	Study design	Country	Population (*n* diagnosis)	IBD (*n* diagnosis)	Prevalence IBD (%)
Mitulescu (2015) [68]	Retrospective	Romania	70 SA	1 IBD	1·4
			39 PsA	0 IBD	0
			17 USPA	2 IBD	11·8
Rudwaleit (2011) [73]	Prospective cohort	Multi-national	176 pSpA	6 IBD	3·4
Essers *et al.* (2015) [66]	Prospective cohort	The Netherlands Belgium France	216 SA	15 IBD	23·6
Dougados (2015) [63]	Prospective cohort	France	708 AxSpA	35 IBD	4·9
Deesomchok (1985) [61]	Retrospective cohort	Thailand	46 SA	0	0
Eliakim (2005) [65]	Prospective cross-sectional	Israel	20 SpA	6 CD-like lesions endoscopic findings	30
Dean (2016) [60]	Registry	Scotland	1964 AS primary care	118 IBD	6
			1700 secondary care	204 IBD	12
Perez Alamino (2011) [70]	Retrospective	Multi-national	1274 AS	45 IBD	3·6
Collantes (2007) [58]	Registry	Spain	1385 SpA	13 IBD	0·3
Buschiazzo (2011) [57]	Prospective cohort	Argentina	402 SpA	10 IBD	2·5
Sampaio-Barros (2011) [75]	Prospective cohort	Italy	1036 SpA	10 IBD	1
Peluso (2015) [69]	Retrospective	Italy	387 PsA	63 IBD	16·2
				15 CD	3·8
				10 UC	2·5
				38 Non-specific colitis	9·8
Rojas-Vargas (2009) [71]	Retrospective	Spain	150 SpA	4 IBD	2·6
Costello (1980) [59]	Prospective	USA	55 SA	9 IBD	16·3
				3 CD	5·45
				6 UC	10·9
Edmunds (1981) [64]	Prospective	UK	1331 SA	82 IBD	6
Tayel (2012) [77]	Registry	Egypt	75 SpA	1 IBD	1·3
del Río-Martínez (2016) [62]	Registry	Spain	291 AxSpA	9 IBD	3·1
			86 pSpA	1o IBD	11·6
Stolwijk (2015) [76]	Registry	UK	4101 SA	151 IBD	3·7
Said-Nahal (2000) [74]	Retrospective	France	329 SpA	17 IBD	5
				10 CD	3
				7 UC	2
García-Vicuña (2016) [67]	Prospective cohort	Spain	513 SpA	13 IBD	2·5

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; SpA = spondyloarthritis; AxSpA = axial spondyloarthritis; pSpA = peripheral spondyloarthritis; USpA = unclassified SpA; AS = ankylosing spondylitis; SA = sacroiliitis; PsA = psoriatic arthritis.

The participants also approved the need for at least three minor criteria for specialist referral in both cases (rheumatological referral of patients with IBD to, and gastroenterological referral of, patients with SpA).

Discussion

The identification of patients with co-existing IBD and SpA may have important implications for their clinical management by influencing treatment, preventing possible complications and, thus, improving clinical outcomes and quality of life. Multi-disciplinary collaboration between gastroenterologists and rheumatologists represents the best way to improve the therapeutic approach to such complex clinical scenarios.

This study identified several red flags for prompt and appropriate referral between gastroenterologists and rheumatologists, which might potentially facilitate the diagnosis of co-existing IBD-SpA.

The results from our systematic review first confirmed the high prevalence of co-existing IBD-SpA, particularly in the gastroenterological population (Table 3). The impact of this association is particularly relevant for the clinical management of IBD patients because articular involvement often requires more expensive or aggressive therapeutic approaches, including biological agents or combination treatment with immunosuppressants (i.e. methotrexate). Moreover, van der Have and colleagues recently showed that the presence of joint pain might significantly and negatively affect the quality of life and the work productivity of IBD patients [88]. The prevalence of IBD in the rheumatological setting seems to be lower, but clinically significant even so (Table 4). The importance of identifying co-existing IBD among

Table 5. Classification of red flags as 'major' or 'minor' criteria for specialist referral

Red flags in SpA	Criteria classification	Red flags in IBD	Criteria classification
Chronic diarrhoea	Major	Chronic low back pain	Major
Rectal bleeding	Major	Dactylitis	Major
Perianal fistula/abscess	Major	Enthesitis	Major
Chronic abdominal pain	Major	Peripheral joint pain/swelling	Major
Nocturnal symptoms	Major	Family history of SpA	Minor
Oral aphtosis	Minor	Psoriasis	Minor
Fever	Minor	Anterior uveitis	Minor
Anaemia	Minor	Chest pain	Minor
Family history of IBD	Minor	Urethritis/cervicitis	Removed
Weight loss	Minor		

IBD = inflammatory bowel disease; SpA = spondyloarthritis.

these patients also derives from the possibility of developing chronic intestinal inflammation during treatment with etanercept, a tumour necrosis factor (TNF) inhibitor specifically used in rheumatology and dermatology [89]. Moreover, the diagnosis of co-existing IBD-SpA may influence the dosage and infusion regimen of most biological agents, because gastroenterological diseases require higher doses in comparison with those used for the treatment of isolated SpA [7].

Very scarce evidence emerged from the literature search concerning the diagnostic accuracy of red flags. No studies could be found specifically in the gastroenterological or rheumatological setting, and a very limited number of studies performed in the general population were identified. In particular, sensitivity and specificity of gastrointestinal red flags for the diagnosis of IBD have been described in only three papers [8,78,79]. Ford *et al.* [78] prospectively enrolled 1981 consecutive patients attending the gastroenterological clinic of two Canadian hospitals because of gastrointestinal symptoms. All subjects underwent a full colonoscopy and were invited to describe their intestinal symptoms among a list selected from the Rome III diagnostic questionnaire [90]. Three hundred and two patients were diagnosed with IBD, whereas all the others (n = 1679) served as controls. The items that resulted in independent predictors of IBD were: positive family history, younger age, the passage of stools more than four times a day >75% of the time, urgency most of the time and anaemia. However, the authors concluded that individual items were not useful to predict a diagnosis of IBD, because most of them had low sensitivity and specificity values [78]. Danese and colleagues [8] identified several red flags to be included in a 21-item questionnaire and administered it to 85 CD patients, 80 subjects with IBS (irritable bowel syndrome) and 36 healthy controls, asking to select the symptoms they had had during the 12 months before the diagnosis (for CD) or at the time of the visit (for IBS and controls). Interestingly, all red flags included in our study were significantly more frequent in the CD patients evaluated by Danese *et al.* [8] Finally, the authors proposed an index with high predictive value for CD diagnosis, based on the eight items that resulted independent at the multivariate analysis, to be validated in prospective studies [8]. The study published by Lisciandrano *et al.* described the pattern of oral lesions in IBD patients and controls, without showing any statistically significant difference among groups [79].

The ASAS (Assessment of SpondyloArthritis International Society Group) developed sets of criteria for the classification of peripheral and axial (with and without definite radiographic sacroiliitis) SpA. The clinical history included features of inflammatory back pain (IBP) and extraspinal manifestations such as arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's/ulcerative colitis, good response to non-steroidal anti-inflammatory drugs (NSAIDs), family history for SpA, human leucocyte antigen (HLA)-B27 and elevated C-reactive protein (CRP). In accordance with these criteria, a patient with chronic back pain (>3 months) and age at onset less than 45 years can be classified in the presence of sacroiliitis plus at least one typical SpA feature, or in the presence of HLA-B27 plus at least two other SpA features. Patients with arthritis and/or enthesitis and/or dactylitis plus one or more of the following parameters – psoriasis, inflammatory bowel disease, preceding infection, HLA-B27, uveitis, sacroiliitis on imaging – or two or more other parameters – arthritis, enthesitis, dactylitis, inflammatory back pain in the past, family history of SpA – can be classified as 'peripheral SpA'. In the entire ASAS population of 975 patients, sensitivity and specificity of the combined use of the two sets of criteria for peripheral SpA were 79·5 and 83·3%, respectively [86]. Tomero *et al.* analysed the performance of the ASAS criteria for the classification of SpA in early SpA clinics. The sensitivity and specificity of the ASAS criteria set were 65 and 93%, respectively, suggesting how these criteria are limited to detection of early SpA forms, especially in

populations in which magnetic resonance imaging (MRI) is not routinely available or in populations with a low prevalence of HLA-B27 [87].

For the early diagnosis of axSpA, the Berlin diagnostic algorithm has been proposed in patients with IBP. This algorithm is completely based on the sensitivity and specificity of typical SpA features and considers the probability of SpA by calculating the likelihood ratio-product of SpA features for each patient. Although the algorithm consists of different steps, the presence of IBP is mandatory. It means that this algorithm is not helpful in the detection of the disease in patients with axSpA but without IBP [85,91]. For this reason, Van der Berg *et al*. validated a modified algorithm for diagnosing axSpA in which IBP is excluded as obligatory entry criterion and added as an SpA feature [80].

Although such scarce data represent an important limitation for any possible evidence-based recommendation, the appropriateness of each red flag was assessed by expert opinion and expressed and quantified using the RAND/UCLA method [11]. After the two rounds of the online survey, there was no disagreement among the participants. However, the interspecialist referral was judged as always appropriate for some red flags and possibly appropriate for others, leading to their classification as 'major' or 'minor' criteria, respectively. In fact, the establishment of some rules for referral may avoid diagnostic delay, improve quality of care and decrease the possibility of complications, but it is also fundamental to avoid clinic overflow with unnecessary referrals and the possible consequent increase of health-care costs. In this regard, we recognize as a limitation of this study the inclusion of some general symptoms in the list of red flags: in particular, our definition of low back pain intentionally excluded any inflammatory characteristic (such as onset before the age of 45, morning stiffness, pain relieved by movements), as well as peripheral joint pain without swelling. However, patients should be referred to the rheumatologist only when these symptoms recur or last for at least 3 months (Table 1). In fact, IBD patients with back/joint pain have a significantly lower quality of life and work productivity [88], therefore these symptoms, when persistent, are worthy of referral to a rheumatologist, regardless of the presence of articular inflammation.

During the last meeting, it was established that at least three minor criteria are required for specialist referral. However, most of the participants argued that some minor red flags have different importance in clinical practice. For example, the family history of IBD is not enough to refer a patient with SpA to the gastroenterologist, but it should be considered more clinically relevant than isolated fever or oral aphthosis; in this case, non-invasive tests such as fecal calprotectin or bowel ultrasound may be indicated to investigate the presence of intestinal inflammation, with subsequent referral to the gastroenterologist only in the case of altered test results.

Similar considerations emerged from minor criteria for rheumatological referral. Non-infectious anterior uveitis, confirmed by the ophthalmologist, may be itself an extra-intestinal manifestation in patients with IBD, regardless of the presence of SpA, and thus should be considered with more caution in comparison with family history of SpA or chest pain.

The strength of our project was the joint involvement of rheumatologists and gastroenterologists in the management of patients with both diseases, and a structured method to collect expert opinion. The main limitation is the lack of reliable evidence to elaborate a solid decision strategy: prospective and multi-centre studies are needed to formally validate these symptoms and signs as diagnostic tools and to combine individual red flags into a 'diagnostic score'. Moreover, the participants in our project came from an Italian setting only; the appropriateness of these criteria may be different in other populations and health-care systems. In this regard, a Spanish study has been published recently, describing some major or minor criteria for diagnosis of SpA or IBD [92]: the results differ slightly from ours. However, this confirms the need for a shared strategy to diagnose such complicated diseases early.

In conclusion, our study suggests that several signs and symptoms should be closely monitored to improve the clinical management of patients with a suspected association of IBD and SpA. Prospective validation of these red flags is necessary before their routine use in clinical practice.

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Author contributions

C. F. and P. L. performed the literature review. L. S. performed the statistical analysis. C. F., P. L. and L. S. wrote the manuscript. E. L., F. C., F.Cast., P. G., A. O., C. S., R. S., M. V., I. O. and A. A. are members of the steering committee of the Italian SpA-IBD Expert Panel Group and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Dedication

We remember with fondness Professor Ignazio Olivieri for his professionalism and compassion.

Disclosures

C. F. has served as a consultant or advisory member for AbbVie and MSD. F. Cast. has served as a consultant or advisory member for AbbVie, Ferring, Janssen, MSD, Sofar and Takeda. P. G. received honoraria or consultation fees from Janssen, Abbvie, Pfizer, Celgene, Takeda, Ferring, MSD, Alfa Wasserman and Amgen; and participated in a company-sponsored speaker's bureau for Abbvie, Janssen, Takeda, Ferring, Msd, Sofar and Chiesi. A. O. served as advisory board member for AbbVie, Janssen-Cilag, MSD, Pfizer and Takeda Pharmaceuticals, and received lecture grants from AbbVie, Chiesi, Janssen-Cilag, MSD, Sofar and Takeda Pharmaceuticals. M. V. participated in the Advisory Board and received lecture fees or support for research from MSD, Hospira, Mundipaharma, Takeda, Abbvie, Chiesi, Zambon, Amgen, Biogen, Jannsen, Pfizer, Sofar and Giuliani. A. A. has served as a consultant or advisory member for AbbVie, Allergan, Amgen, Biogen, Celgene, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Pfizer, Samsung Bioepis, Sofar and Takeda, has received lecture fees from AbbVie, AstraZeneca, Chiesi, Ferring, Hospira, Medtronic, MSD, Mitsubishi Tanabe, Mundipharma, Nikkiso, Otsuka, Pfizer, Samsung Bioepis, Takeda, Tigenix, and Zambon, and has received research funding from MSD and Takeda. All other authors have no conflicts of interest to declare.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Fig. S1. Flowchart of study selection for diagnostic accuracy of gastrointestinal red flags.

Fig. S2. Flowchart of study selection for diagnostic accuracy of rheumatologic red flags.

APPENDIX 1

Collaborators

Italian SpA-IBD Expert Panel Group:

- Marina Beltrami, Department of Internal Medicine, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy
- Fabrizio Bossa, Division of Gastroenterology, 'Casa Sollievo della Sofferenza' Hospital, IRCCS, San Giovanni Rotondo, Foggia, Italy
- Francesco Costa, Gastroenterology Unit, Department of Gastroenterology, University of Pisa, Pisa, Italy
- Walter Fries, Inflammatory Bowel Disease Unit, A.O.U. Policlinico 'G. Martino', Messina, Italy
- Mauro Galeazzi, Department of Medical Sciences, Surgery and Neurosciences, Rheumatology Unit, University of Siena, Siena, Italy
- Roberto Giacomelli, Division of Rheumatology, Department of Biotechnological and Applied Clinical Science, University of L'Aquila, L'Aquila, Italy
- Giovanni Lapadula, Rheumatology Unit, Department of Emergency and Transplantation, University of Bari, Bari, Italy
- Nazzarena Malavolta, Departmental Program of Rheumatology, Cardio-Thoraco-Vascular

Department, Azienda Ospedaliera Universitaria di Bologna, Bologna, Italy
- Mariabeatrice Principi, Gastroenterology Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), University of Bari, Italy
- Roberta Ramonda, Rheumatology Unit, Department of Medicine-DIMED, University Hospital of Padova , Padova , Italy
- Gabriele Riegler, U.O.S.D. of Gastroenterology - 'Luigi Vanvitelli' Campania University, Naples, Italy
- Giovanni Triolo, Rheumatology Section, Department of Internal Medicine, University of Palermo, Palermo. Italy
- Giorgio Zoli, Department of Internal Medicine, SS Annunziata Hospital, Cento, Ferrara, Italy