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Abstract

Background: Occurring in approximately 20 to 30% of patients, spondyloarthritis is the most common extraintestinal manifestation in inflammatory bowel disease (IBD).

Aims: To look for risk factors of spondyloarthritis among inflammatory bowel disease patients.

Methods: We modified the STRIPP questionnaire created for psoriatic patients and we created a rapid questionnaire for rheumatologic investigation in IBD patients (STRII). We submitted the questionnaire to all consecutive patients with a known spondyloarthritis in our centre and to patients with a negative rheumatological diagnosis to find the cut-off value. Finally, we prospectively submitted the STRII questionnaire to all consecutive IBD patients in our centre.

Results: A cut-off >= 3 correlated with spondyloarthritis with an AUC = 0.91. The STRII questionnaire was submitted to 1147 IBD patients. Two hundred and forty-four out of 1147 (21.3%) collected a STRII score of >= 3. Female sex ($p < 0.0001$) and Crohn's disease ($p = 0.023$) were risk factors. Patients with a history of at least 1 immunosuppressant or biologic drug ($p = 0.002$ and $p < 0.0001$, respectively) had a higher rate of positivity to STRII questionnaire.

Conclusion: Among IBD patients, females, Crohn's disease, those with an history of at least 1 immunosuppressive or biological therapy are at increased risk of spondyloarthritis.

Key Words: Arthritis; Extra-intestinal manifestations; Questionnaire; Rheumatologic; STRII

1 Introduction:

It is increasingly clear that inflammation in inflammatory bowel disease (IBD), although expressed mainly in the gut, is not limited to this organ, and the concept of “syndrome” is now accepted [1].

The articular manifestations, occurring about in 20-30% of IBD patients, are the more frequent extraintestinal manifestations in IBD patients [2,3]. These are classically divided in axial and peripheral spondyloarthritis (SpA). The former includes nonradiographic sacroiliitis and ankylosing spondylitis, the latter is subdivided, according to the number of joints involved, in type 1 (if <=5) or type 2 [4].

Despite the development of the assessment of spondyloarthritis international society (ASAS) classification criteria [5], the delay for the diagnosis of SpA in IBD is still unacceptably long (8 to 11 years after the onset of symptoms [6]). Furthermore, not all gastroenterologists actively ask to IBD patients if they suffer from symptoms suspected for SpA.

The number of questionnaires studied to find the SpA in IBD is fairly limited [7–12], as well as the number of studies that have search for which IBD patients are at increased risk of associated arthropathy [2,13]: only three studies specifically developed a questionnaire to find SpA in IBD and none correlated the findings with immunosuppressants or biologics use.

The aim of our study was to look for risk factors for suspected SpA in IBD patients applying rapid questionnaire to find the patients suffering from SpA among IBD patients.

2 Material and Methods:

Given the similarity between psoriasis-associated and IBD-associated SpA, we modified the questions of the “Screening Tool for Rheumatologic Investigation in Psoriatic Patients” (STRIPP) questionnaire [14], an Italian, light, self-administered, questionnaire able to identify patients who need a rheumatologic consultation among psoriatic patients (with a specificity of 93.3% and a sensitivity of 91.5% taking a point of 3.5 as a cut-off). The English translation of the questions of our questionnaire are reported in **Table 1**.

Table 1.

The score assigned to the single questions was adapted by those of the STRIPP questionnaire by an expert panel composed by two gastroenterologist (A.M., D.G.R.) and three rheumatologists (E.F., S.P., M.C.D.) [14].

In the first phase, we submitted the questionnaire to all consecutive patients of our IBD centre with a known SpA (patients identified as suffering from SpA were evaluated and certified by a rheumatologist) and to a double number of consecutive patients with a negative diagnosis for SpA (according to current classification criteria for SpA) to find the cut-off value for suspected SpA.

In the second phase we prospectively submitted the Screening Tool for Rheumatologic Investigation in Inflammatory bowel disease (STRII) questionnaire to all consecutive IBD patients of our outpatient clinic to look for risk factors of suspected SpA among IBD patients. Since some risk factors are already known (many studies have shown that symptoms of peripheral arthritis

are related to intestinal disease activity, whereas axial involvement is independent of bowel inflammation activity, family history of IBD, appendectomy, cigarette smoking, and the presence of other extra-intestinal manifestations, such as erythema nodosum or pyoderma gangrenosum, duration of disease [15]), we focused on age, sex, anaemia, associated dermatological inflammatory disease, use of immunosuppressants or biologics.

We read the questions to the patients and we scored the results on the sheet which included the 5 questions.

For first phase the inclusion criteria were:

- Patients followed at our outpatients IBD clinic with a previous rheumatological visit that concluded in favour or against a SpA diagnosis (according to spondyloarthritis international society (ASAS) criteria [16]).

For the second phase the inclusion criteria were:

- IBD confirmed diagnosis (at least 1 year of follow up with at least two endoscopic or imaging tests confirming the diagnosis).

Exclusion criteria were:

- A previous diagnosis of gouty arthritis, rheumatoid arthritis, connective tissue disease, inflammatory myopathy, rheumatic polymyalgia, Sjogren's syndrome.

2.1 Statistics

Continuous variables were expressed as mean ± standard deviation (SD). The Chi-square, or Fisher's exact test when appropriate, and the non-parametric

Mann-Whitney U test were applied for categorical and continuous variables respectively. The question how accurate STRII questionnaire was in identifying SpA in IBD was evaluated using Receiver Operating Characteristic (ROC) curve analysis. Regarding the sample size, we submitted the STRII questionnaire to all our patients during the study period, in order to broadly exceed the number of the largest study published in the literature [7]. A p value of less than 0.05 was considered significant. The statistical analysis was performed with MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

2.2 Ethical considerations

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

3 Results:

In the first phase we submitted the questionnaire to 426 patients (to all 142 patients with a known SpA, according to ASAS criteria [16], and to 284 with a previous rheumatological visit that concluded against a SpA diagnosis). Demographic characteristics of the two groups are shown in **Table 2**.

Table 2.

At ROC curve analysis, a cut-off >= 3 correlated with a SpA diagnosis with an AUC = 0.91 ($p < 0.001$), sensitivity = 85.2%, specificity 85.5% (**Figure 1**).

Figure 1.

In the second phase, from January 2017 to April 2019, the STRII questionnaire was submitted to 1147 IBD patients. Demographic characteristics of patients are shown in **Table 3**.

Table 3.

Two hundred and forty-four out of 1147 (21.3%) collected a STRII score of >= 3. Ninth-nine out of 1147 (8.6%) already had a diagnosis of arthritis (**Figure 2**).

Figure 2.

Age (median age in IBD patients with STRII score >= 3: 53 years, versus 50 years in IBD patients with STRII score < 3, $p = 0.11$) was not a risk factor for a suspected SpA.

Female sex (29.4% of females had a STRII score >= 3, versus 14.8% of the males, $p < 0.0001$) and type of IBD (23.5% of Crohn's disease (CD) patients had a STRII score >= 3, versus 17.9% of ulcerative colitis (UC) patients, $p = 0.023$) were a risk factor for SpA in IBD patients.

Patients with symptoms suspected for SpA (i.e. STRII score >= 3) suffered from higher rates of anaemia (defined as haemoglobin levels < 12 g/dl in women and < 13 g/dl in men) (22.7% versus 14.3% in IBD patients with STRII score < 3, p = 0.026), and associated inflammatory dermatological diseases (erythema nodosum, pyoderma gangrenosum, hidradenitis suppurativa) (23% versus 12.1% in IBD patients with STRII score < 3, p = 0.022).

Patients with a history of at least 1 immunosuppressive (azathioprine, mercaptopurine, methotrexate) treatment for IBD had a higher rate of positivity to STRII questionnaire (26.9% versus 18.8%, p = 0.002). Patients with a history of at least 1 biological (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) therapy for IBD had a higher rate of positivity to STRII questionnaire (33.6% versus 18.1%, p < 0.0001).

4 Discussion:

A direct link between the bowel and the joints inflammation seems to exists, mediated by a T helper (Th)-17 pathway [17].

Several years of diagnostic delay of SpA in IBD [6] is an hardly acceptable status quo. An early diagnosis of SpA and the consequent start of an anti-tumor necrosis factor (TNF) therapy could change the natural history of the SpA, at least for axial-SpA [15,16].

Among the few questionnaires studied to find SpA in IBD, D'Incà et al [7] published a study in which a self-administered questionnaire, consisting of as many as 31 questions, was completed by IBD patients. The authors said that the questionnaire was previously validated in a small sample, but they have not

reported us any details about the validation process. They found a prevalence of IBD-associated SpA of 40.2% if the whole life was considered, of 9.5% if only the last year was considered.

The Toronto axial spondyloarthritis questionnaire has been developed to search only for axial-SpA in IBD [8].

Shortage of time is cited as the main barrier against actively seeking among all IBD patients those who are also affected by SpA.

In this regard, to be really applicable in daily out-patients clinical activity, a questionnaire must be rapid to apply (5-8 questions, few minutes to complete it [18], yes or no answers, easy to understand, without the need for laboratory or imaging tests). The STRII questionnaire has been developed according to these criteria.

The STRII questionnaire seems to be effective in the search for SpA (AUC = 0.91, $p < 0.001$).

The prevalence of SpA in IBD (21.3%) is in agreement with the data present in the literature [7]. Only 99 out of 1147 (8.6%) already had a diagnosis of arthritis: this mean that about 60% of patients with symptoms suspected for arthritis did not have yet a diagnosis of arthritis.

The data present in literature regarding risk factors for SpA in IBD support no gender difference [2] and UC versus CD [13]. Conversely, our prospective results in a large sample (1147 patients analysed) strongly support in favour of female sex as a risk factor for SpA in IBD (29.4% of females had a STRII score >= 3, versus 14.8% of the males, $p < 0.0001$) and moderately in favour of CD

as a risk factor of SpA versus UC (23.5% of CD patients had a STRII score >= 3, versus 17.9% of UC patients, p = 0.023).

From our study emerged that patients with a suspected rheumatological comorbidity (i.e. SpA) suffer in higher percentage from anaemia and are at higher risk for a third inflammatory comorbidity (i.e. a dermatological inflammatory disease).

Our study searched for a link between the use of immunosuppressants or biologic therapy for IBD and the prevalence of an associated SpA: patients with a history of at least 1 immunosuppressive treatment for IBD had a higher risk for SpA (26.9% versus 18.8%, p = 0.002), and the same was true for biological therapy (33.6% versus 18.1%, p < 0.0001) (data in accordance with those of a study that specifically looked at IBD patients on TNF inhibitors [19]).

Some limitations of our study must be discussed. One might wonder if a part of the positive results of our questionnaire cannot derive from arthralgia and not from inflammatory arthropathies, but the good correlation between a score >= 3 at the STRII questionnaire and a previous diagnosis of an inflammatory arthropathy (patients identified as suffering from SpA were evaluated and certified by a rheumatologist according to ASAS criteria [16]) (AUC = 0.91) should reduce this bias. Fibromyalgia remains the real diagnosis that cannot be carefully distinguish by a questionnaire [20,21], because pain is in common between fibromyalgia and Spa, and the term “pain” is present in 3 of the 5 questions of the STRII questionnaire. Only the rheumatologist, to which the patients will be referred, will be able to do the differential diagnosis with fibromyalgia. It would be interesting to differentiate between axial and peripheral

spondyloarthritis as the risk factors could be different (“women with SpA more frequently show peripheral joint involvement, whereas men tend to have axial involvement." [15]). In the first phase of our study we correlated the total score deriving from the 5 questions with a diagnosis of peripheral or axial SpA and we found a cut-off of >= 3 points. Our questionnaire was not validated to search specifically for axial o peripheral SpA, so we cannot differentiate them. This could be the aim of a future study.

5 Conclusions:

In conclusion, most of the patients with suspected SpA (STRII score >= 3) have not yet a diagnosis of SpA. Among all IBD patients, females, CD, patients with an history of at least 1 immunosuppressive or biological therapy are those at higher risk of a coexistent SpA. These patients are those that should be subjected to a questionnaire like the STRII (active search for SpA): patients with a positive result (i.e. >= 3) should be referred to a rheumatologist.

Conflicts of Interest Statement

None to declare.

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Table 1. English translation of the questions of the STRII questionnaire

	Score
Have you ever had a finger completely swollen like a sausage without trauma?	**2**
Have you ever had pain/swelling in your heel or Achilles tendon? OR Have you ever had pain/swelling in your knees (without trauma) or hands?	**2**
Have you ever had periods of back pain, which improve with movement and are accentuated with rest, possibly waking you up at night, for at least 3 consecutive months	**2**
Have you ever used anti-inflammatory drugs for the aforementioned problems for a period of several months	**1**
Have you ever suffered from episodes of pain/joint stiffness of over 30 minutes when you wake up, that improve with the movement?	**2**

STRII = Screening Tool for Rheumatologic Investigation in Inflammatory bowel disease

Table 2. Demographic characteristics of the patients included to find the cut-off for SpA (n = 426)

Demographic characteristic	**Positive for SpA**	**Negative for SpA**	**p value**
n of patients	142	284	N/A
Median age (years)	52	55	0.29
Male/Female	60/82	170/114	0.02

SpA = spondyloarthritis; n = number; N/A = not applicable

Table 3. Demographic characteristics of the included patients

Demographic characteristic	**Data**
n of IBD patients	1147
Median age (years)	51 ± 7.9
Male/Female	641/506
UC/CD	453/694

n = number; IBD = inflammatory bowel disease;

UC = ulcerative colitis; CD = Crohn's disease

Figure 1. Ability of the STRII questionnaire to search for SpA (ROC curve for sensitivity and specificity of the STRII)

Figure 2. Percentage of the patients with a known diagnosis of SpA among the patients with a suspected SpA (STRII score >= 3)