

Identifying Axial Spondyloarthritis in Patients With Inflammatory Bowel Disease Using Computed Tomography

Chong S.E. Lim¹ , Louise Hamilton¹, Samantha B.L. Low², Andoni Toms², Alexander Macgregor¹, and Karl Gaffney¹

ABSTRACT. Objective. The diagnosis of axial spondyloarthritis (axSpA) is hampered by diagnostic delay. Computed tomography (CT) undertaken for nonmusculoskeletal (non-MSK) indications in patients with inflammatory bowel disease (IBD) offers an opportunity to identify sacroiliitis for prompt rheumatology referral. This study aims to identify what proportion of patients with IBD who underwent abdominopelvic CT for non-MSK indications have axSpA and to explore the role of a standardized screening tool to prospectively identify axSpA on imaging.

Methods. Abdominopelvic CT scans of patients with verified IBD, aged 18 to 55 years, performed for non-MSK indications were reviewed by radiologists for the presence of CT-defined sacroiliitis (CTSI), using criteria from a validated CT screening tool. All patients identified were sent a screening questionnaire, and those with self-reported chronic back pain (CBP), CBP duration of greater than 3 months, and age of onset of less than 45 years were invited for rheumatology review.

Results. CTSI was identified in 60 out of 301 (19.9%) patients. Out of these 60 patients, 32 (53%) responded to an invitation to participate, and 27 out of 32 (84.3%) were enrolled. Of these, 8 had a preexisting axSpA diagnosis and 5 did not report CBP. In total, 14 patients underwent rheumatology assessment, and 3 out of 14 (21.4%, 95% CI 4.7-50.8) had undiagnosed axSpA. In total, 11 out of 27 (40.7%, 95% CI 22.4-61.2) patients had a rheumatologist-verified diagnosis of axSpA.

Conclusions. In this study, 5% (3/60) of patients with IBD undergoing abdominopelvic CT for non-MSK indications with CTSI were found to have undiagnosed axSpA and, overall, 18.3% (11/60) were found to have axSpA. This reveals a significant hidden population of axSpA and highlights the need for a streamlined pathway from sacroiliitis detection to rheumatology referral.

Key Indexing Terms: ankylosing spondylitis, axial spondyloarthritis, computed tomography, inflammatory bowel disease, sacroiliitis

Extramusculoskeletal manifestations, including acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis, are common among patients with axial spondyloarthritis (axSpA), and referral strategies have been published for AAU in order to reduce delay to diagnosis.¹⁻³ Delayed diagnosis leads

to worse outcomes for people with the disease.^{4,5} To our knowledge, there are no published imaging referral strategies for patients with IBD to assess for concurrent clinically diagnosed axSpA.

Patients with IBD often undergo imaging to evaluate their gastrointestinal disease, thereby presenting an opportunity to trigger a rheumatology referral in those with sacroiliitis on imaging. Computed tomography (CT) is one method for identifying sacroiliitis. Recent evidence has shown that the prevalence of sacroiliitis as identified by CT performed in patients with IBD for nonmusculoskeletal (non-MSK) indications ranges from 2.2% to 25%.⁶⁻⁹ In parallel, a practical CT screening tool has been developed to differentiate sacroiliitis in (1) patients with axSpA vs controls,¹⁰ and (2) patients with IBD vs controls,⁹ which could potentially be used to identify axSpA in patients with IBD. To our knowledge, there are no studies reporting on the proportion of patients with IBD with CT-defined sacroiliitis (CTSI) who have subsequently been diagnosed as having axSpA by a rheumatologist, defined here as a rheumatologist-verified diagnosis of axSpA (RVD-axSpA).

This study explores the frequency of undiagnosed and diagnosed axSpA in this population and the utility of a CT screening tool¹⁰ to expedite axSpA diagnosis in the IBD population

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¹C.S.E. Lim, MBBS, Consultant Rheumatologist, L. Hamilton, MD, Consultant Rheumatologist, A. Macgregor, PhD, Consultant Rheumatologist, K. Gaffney, MB BCh BAO, Consultant Rheumatologist, Rheumatology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust; ²S.B.L. Low, MBBS, Consultant Radiologist, A. Toms, PhD, Consultant Radiologist, Radiology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK.

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Address correspondence to Dr. C.S.E. Lim, Rheumatology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, NR4 7UY, UK. Email: edwin.lim@nmuh.nhs.uk, esclim@gmail.com.

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through the identification of CTSI using scans performed for non-MSK indications.

METHODS

Design. This study was cross-sectional in design. Patients with IBD who were retrospectively identified to have CTSI underwent a prospective clinical assessment to determine what proportion had RVD-axSpA (Figure).

Identification of the study population. The study population was selected from a service evaluation project performed at a large academic teaching hospital.

Abdominopelvic CT scans of patients with IBD—Crohn disease or ulcerative colitis—that were obtained between January 2010 and December 2017 were retrospectively identified from the radiology imaging system. The diagnosis of gastroenterologist-verified IBD was confirmed with clinical records. The study population was limited to those 18 to 55 years of age, inclusive, at the time of their CT, with their most recent CT named the index scan. The scans were reviewed by radiologists trained to identify radiological features of CT-defined sacroiliitis, using the criteria developed by Chan et al,¹⁰ after internal reliability testing and clarification (for more details, see Supplementary Table S1, available with the online version of this article).

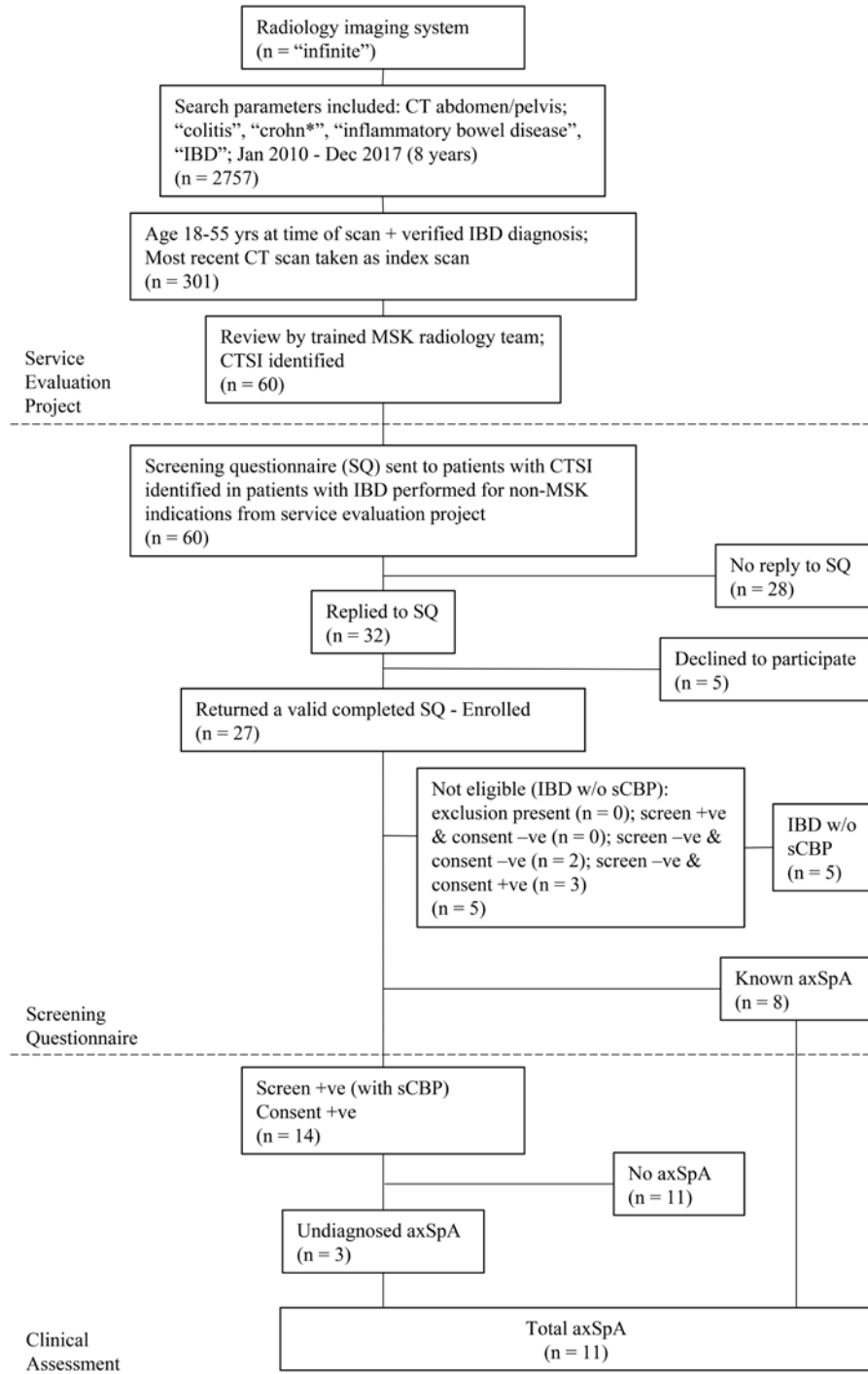


Figure. Flowchart of the study. -ve: negative; +ve: positive; axSpA: axial spondyloarthritis; CT: computed tomography; CTSI: computed tomography-defined sacroiliitis; IBD: inflammatory bowel disease; MSK: musculoskeletal; sCBP: self-reported chronic back pain with duration of > 3 months and age of onset of < 45 years; w/o: without.

Study population. Screening questionnaires (SQs) were sent to all patients with IBD who had a CT performed for non-MSK indications; were between the ages of 18 and 55 years, inclusive, at the time of their CT; and were identified as having CTSI.

CTSI is defined as the presence of sacroiliac joint ankylosis, total erosion score (TES) ≥ 3 , > 0.5 -cm iliac sclerosis, and/or > 0.3 -cm sacral sclerosis (for more details, see Supplementary Table S2, available with the online version of this article). As our sampled population was enriched with patients with an IBD diagnosis and an age range of patients with the highest diagnostic yield for axSpA, we selected the criteria that were shown to have the highest sensitivity (94%) by Chan et al¹⁰ to identify cases of sacroiliitis that were suspected to co-occur with axSpA, so that all possible cases were included.

Subjects who replied with a valid completed SQ and gave informed consent were enrolled. Those with chronic back pain (CBP) lasting > 3 months and with an age of onset < 45 years were invited for rheumatology assessment. Patients with preexisting confirmed axSpA, as verified from their medical records, were contacted by telephone to collect clinical characteristics, but these patients were not reassessed. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (252117 19/EE/0125). All participants gave written informed consent before study inclusion.

Clinical assessment. Clinical assessment included a full medical interview; physical examination by a rheumatologist, including joint and tender point count, the Maastricht Ankylosing Spondylitis Enthesitis Score, dactylitis count, and the Bath Ankylosing Spondylitis Metrology Index^{11,12}; patient-reported outcomes, including the Bath Ankylosing Spondylitis Disease Activity Index, the Bath Ankylosing Spondylitis Functional Index, the Bath Ankylosing Spondylitis Global score, the Harvey-Bradshaw Index, and the Partial Mayo Index^{11,13,14}; laboratory tests, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and HLA-B27; and dedicated magnetic resonance imaging (MRI) sequences for axSpA detection.¹⁵

Diagnosis verification. Each subject was discussed in 2 virtual meetings: an initial discussion solely based on clinical history and examination findings and a second discussion following the availability of laboratory and imaging results. The panel comprising 3 rheumatologists with a specialist interest in axSpA were blinded to the CT findings. Each made either a positive or negative diagnosis of axSpA. They also indicated their level of diagnostic confidence on a 10-point Likert scale. RVD-axSpA was confirmed when at least 2 of 3 rheumatologists agreed. The level of confidence (LoC) was reflected by an average of the 3 Likert scales. A similar process was undertaken when the results of the MRI and laboratory results were available. Any discrepancy between the pre- and postinvestigation diagnosis was discussed in a further summary meeting, and a final diagnosis was made by a majority consensus vote after a subsequent review of all clinical, laboratory, and MRI information.

Definition of the CT screening tool and retrospective analysis. The presence of sacroiliac joint ankylosis or a TES ≥ 3 was determined by Chan et al¹⁰ to be sufficient for identifying patients as having sacroiliitis with suspected axSpA that may warrant a rheumatologist referral (for more details, see Supplementary Table S3, available with the online version of this article). A retrospective exploratory analysis of our study data using the CT screening tool definition was performed to understand the efficacy of the tool in predicting a final diagnosis of axSpA.

Power calculation and statistical analysis. Estimates of the proportion of RVD-axSpA in those patients with IBD with CTSI were unknown. Instead, sample size was estimated from symptomatic CTSI (a range of 3-45%).¹⁶⁻¹⁸ It was estimated that 21 patients were needed to detect a minimum symptomatic CTSI proportion of 30%—derived from clinical experience at our institution—at a nominal threshold significance of $P = 0.05$. Based on the assumptions that 50% of these patients would respond to the SQ and that 80% of the respondents would take up an invitation for clinical review, the study aimed to screen an initial sample of 54 patients with IBD.

Descriptive statistics were used to summarize the patient characteristics, stratified by symptoms and diagnosis. Interclinician diagnostic agreements were calculated using the κ statistic with estimated CIs. Descriptive statistics were used to present the average LoC. For calculation of proportions, the ratio of the frequency of cases to the base population was used with a calculated CI. The efficacy of the CT screening tool in predicting a final diagnosis of axSpA was measured in terms of sensitivity, specificity, positive predictive value, and negative predictive value. Data analysis was performed using Stata (version 15; StataCorp) and Microsoft Excel 2016.

RESULTS

Service evaluation results. In total, 301 unique scans of patients with verified IBD were reviewed by the radiology team (Figure). A total of 19.9% (60/301) of these patients were identified as having CTSI. Only 15 (25%) of these 60 cases were reported as showing sacroiliitis, with no recommendation made for onward rheumatological evaluation (for full results, see Supplementary Table S4, available with the online version of this article).

Study patient characteristics and axSpA diagnosis. In total, 60 patients were sent an SQ. In total, 32 (53.5%) of these patients responded to the invitation to participate, and 27 out of 32 (84.3%) were enrolled (Figure). The detailed clinical characteristics of these patients are shown in Supplementary Table S5 (available with the online version of this article). Out of 27 patients, 14 (51.9%) were invited for rheumatology assessment, as 8 (29.6%) had a prior diagnosis of axSpA, and 5 (18.5%) did not report CBP. Out of these 14 patients, 3 (21.4%, 95% CI 4.7-50.8) had undiagnosed RVD-axSpA. The other diagnoses included spondylosis (5/14, 36%), fibromyalgia (5/14, 35.7%), and nonspecific lower back pain (1/14, 7.1%). In total, 11 of the 27 (40.7%, 95% CI 22.4-61.2) enrolled patients had RVD-axSpA. See Table 1 for different permutations of various proportions of axSpA/sacroiliitis.

Agreement of RVD-axSpA and LoC. There was moderate agreement (κ 0.42, 95% CI 0.04-0.80), with a median LoC of 6 (IQR 2-8), of RVD-axSpA based on only clinical information before investigative results. Once presented with investigation results (ie, CRP, ESR, HLA-B27, and MRI findings), the agreement changed to fair (κ 0.30, 95% CI 0.00-0.65), with a median LoC of 7 (IQR 3-9). The agreement was substantial (κ 0.74, 95% CI 0.10-0.98), with a median LoC of 7 (IQR 5-8), for discrepant cases after further discussion. For all cases, the final agreement was almost perfect (κ 0.85, 95% CI 0.35-0.97), with a median LoC of 8 (IQR 5-9).

Performance of the CT screening tool. The utility of the CT screening tool was explored in different groups for its performance, retrospectively. The CT screening tool was applied to patients who joined the study regardless of having self-reported CBP (analysis 1: patients asymptomatic and symptomatic with CTSI) vs patients with self-reported CBP, CBP duration of greater than 3 months, and age of onset < 45 years based on the SQ (analysis 2: patients symptomatic with CTSI). These results are shown in Tables 2A,B. The sensitivity, or the ability of the tool to detect patients with RVD-axSpA, was similar for both groups at 90.9%. The specificity values for the groups, or the ability of the tool to correctly reject those without axSpA, were 56.3% and 63.6%, respectively.

Table 1. Proportions of axSpA/sacroiliitis in patients with IBD.

Case Definition	Base Population Definition	Cases, n	Base Population, n	Proportion ^a , %
Undiagnosed axSpA ^b	All patients who had a CA ^c	3	14	21.4
Undiagnosed axSpA	All patients who returned a valid SQ ^d	3	27	11.1
All axSpA	All patients who returned a valid SQ	11	27	40.7
All axSpA	Patients c/o sCBP who had a CA	11	22	50.5
Asymptomatic CTSI (no sCBP)	All patients who returned a valid SQ	5	27	18.5
Symptomatic CTSI (sCBP)	All patients who returned a valid SQ	22	27	81.5
Symptomatic CTSI (sCBP but no axSpA)	All patients who returned a valid SQ	11	27	40.7
All axSpA	All patients who were sent an SQ	11	60	18.3 ^e
Undiagnosed axSpA	All patients who were sent an SQ	3	60	5.0 ^e

^a Proportions are in reference to the Figure; proportion = case / base × 100%. ^b AxSpA refers to RVD-axSpA. ^c CA refers to the group that had a clinical assessment for axSpA either in the study or previously by a rheumatologist. ^d Valid SQ refers to the group that returned a valid completed SQ. ^e This estimate assumes that all other cases in the base population do not have a clinical diagnosis of axSpA. AxSpA: axial spondyloarthritis; CA: clinical assessment; c/o: complaining of; CTSI: computed tomography-defined sacroiliitis; IBD: inflammatory bowel disease; RVD: rheumatologist-verified diagnosis; sCBP: self-reported chronic back pain > 3 months, age of onset < 45 years old; SQ: screening questionnaire.

Table 2A. Participants in each group.

Clinical Diagnosis	Analysis 1 ^a , n			Analysis 2 ^b , n		
	Positive	Negative	Total	Positive	Negative	Total
axSpA	10	1	11	10	1	11
No axSpA	7	9	16	4	7	11
Total	17	10	27	14	8	22

^a Analysis 1 involved applying the screening tool to the group with or without a history of chronic back pain who have an age of onset of < 45 yrs (n = 27). ^b Analysis 2 involved applying the screening tool to the group with a history of self-reported chronic back pain who have an age of onset of < 45 yrs (n = 22). AxSpA: axial spondyloarthritis.

Table 2B. Performance of the screening tool.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	DOR
Analysis 1 ^a	90.9	56.3	58.8	90.0	2.1	0.2	12.9
Analysis 2 ^b	90.9	63.6	71.4	87.5	2.5	0.1	17.5

^a Analysis 1 involved applying the screening tool to the group with or without a history of chronic back pain who have an age of onset of < 45 yrs (n = 27). ^b Analysis 2 involved applying the screening tool to the group with a history of self-reported chronic back pain who have an age of onset of < 45 yrs (n = 22). DOR: diagnostic odds ratio; LR-: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

DISCUSSION

Axial spondyloarthritis is a clinical diagnosis.¹⁹ Asymptomatic, imaging-positive sacroiliitis does not automatically imply a diagnosis of axSpA without physician verification. Sacroiliac joint abnormalities can occur for other reasons, including mechanical or degenerative causes, which can manifest as subchondral sclerosis, vacuum phenomenon, and osteophytosis.^{20,21} In addition, targeted therapy should not be given to patients without a clinical diagnosis of axSpA, regardless of imaging results. This highlights the importance of understanding what proportion of

patients with IBD with CTSI have RVD-axSpA. Referral strategies have been published for AAU,³ and questionnaires have been developed to identify spondyloarthritis, using classification criteria, among patients with IBD.^{22,23} However, there are no published data on the use of CT as a referral strategy with subsequent confirmation of a physician-verified diagnosis of axSpA.

We identified that 60 out of 301 (19.9%) of patients with IBD undergoing CT for non-MSK indications had CTSI, and at least 11 out of 60 (18.3%) had RVD-axSpA. In total, 5% (3/60) were previously undiagnosed, despite a mean interval

since the index CT scan of 5.7 years and mean duration of back pain of 13.7 years. The validated CT screening tool to identify CTSI was shown to have a sensitivity of 90.9% and specificity of 63.6% for a clinical diagnosis of axSpA. Taken together, this suggests that among an IBD cohort, aged 18 to 55 years, with a CBP duration > 3 months and an age of onset < 45 years, the tool would be effective in identifying patients with IBD at the highest risk of having RVD-axSpA.

Previous clinical studies have shown that 3% to 45% of patients with IBD have symptomatic sacroiliitis seen on plain radiographs and/or CT using a broad range of definitions for sacroiliitis.¹⁶⁻¹⁸ These authors also showed that the proportion of asymptomatic sacroiliitis (ie, patients with IBD with sacroiliitis but no back pain) ranged from 13.6% to 32%.^{16,18,24} On the other hand, radiology-based studies found that the proportion of incidental/coincidental sacroiliitis on CT in patients with IBD ranged from 2.2% to 25%.⁶⁻⁹ In our study, 22 out of 27 (81.5%) patients with IBD had symptomatic CTSI: 11 out of 27 (40.7%) had RVD-axSpA (3/11 were undiagnosed and 8/11 had known diagnosis) and 11 out of 27 (40.7%) had symptoms but no RVD-axSpA. We also found that 5 out of 27 (18.5%) patients with IBD had asymptomatic CTSI (Table 1 and Figure).

This study is important for several reasons. First, the design of the study is novel. It involves a cross-sectional postal survey of patients with CTSI, supplemented by a structured clinical assessment of a subset of participants to establish the proportion with RVD-axSpA. This is designed to mirror the real-world scenario, whereby if a patient with IBD undergoing CT scan was found to have suspicious sacroiliac changes on imaging, the responsible clinician—the SQ is the surrogate here—would review the patient before onward referral to rheumatology.

Second, the diagnosis was made by an experienced panel of rheumatologists with a special interest in axSpA, with good diagnostic agreement and a high LoC. Given that there is no gold-standard diagnostic biomarker, the current gold standard is expert opinion. When approaching patients with multisystem complex disease, it can be difficult to make a diagnosis.²⁵ There is a need to distinguish whether the etiology of sacroiliitis, and back pain, is a result of underlying mechanical/degenerative disease and/or psychological pain overlay of a chronic disease; undiagnosed active inflammatory axial disease; or a combination of both. In this cohort (Supplementary Table S5, available with the online version of this article), where the mean disease duration was > 10 years, only 4 out of 9 (44.4%) patients with RVD-axSpA and CTSI had active sacroiliac joint inflammatory lesions on MRI. On the other hand, among patients with a mean disease duration of 17 years with symptomatic CTSI but no diagnosis of RVD-axSpA, none (0/11, 0%) had active sacroiliac joint inflammatory lesions. This could reflect the natural history of inflammatory lesions and highlights the challenges around reliance on structural/inflammatory imaging lesions in making a clinical diagnosis of axSpA in this population.

Third, our study was able to explore the usefulness of a validated imaging tool that may prompt earlier referral to rheumatology, potentially expediting a diagnosis of axSpA. This study shows that by using an objective tool and a self-reported SQ, it

is feasible to filter the large numbers of patients with IBD having CT scans down to those with a high pretest probability of axSpA and arrive at a manageable proportion of patients for clinical assessment. This will ensure that rheumatology services are not overwhelmed and, yet, are able to identify some undiagnosed axSpA.

This study has several limitations. The study had a cross-sectional design, the sample size was small, and this was a single-center study. We focused our sample on the population with the highest probability of axSpA; therefore, it is possible that we missed other cases because of selection bias. Also, 33 out of 60 (55%) patients with CTSI did not complete the SQ or declined to participate (Figure); thus, their data were not captured. This means that the results may not be generalizable and the prevalence of undiagnosed RVD-axSpA may have been underestimated. Our design did not allow for evaluation of those without CBP, some of whom may have had axSpA; however, it is likely that such patients would have a lower symptom burden and not require targeted therapy. Finally, we did not clinically reevaluate those with a preexisting diagnosis of axSpA, so it is theoretically possible that some of these patients could have been misdiagnosed.

In conclusion, the results of this study may have practical implications, as they show that there is still undiagnosed axSpA among patients with established IBD attending a secondary care institution. It also explores the possibility of using a pragmatic CT screening tool to improve disease awareness among radiologists, aid in axSpA identification, and reduce the delay to diagnosis in this population. The practicalities of implementing this strategy on a wider scale in routine practice will need further research.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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