Fat Infiltration on Magnetic Resonance Imaging of the Sacroiliac Joints Has Limited Diagnostic Utility in Nonradiographic Axial Spondyloarthritis

Ulrich Weber, Susanne J. Pedersen, Veronika Zubler, Kaspar Rufibach, Stanley M. Chan, Robert G.W. Lambert, Mikkel Østergaard, and Walter P. Maksymowych

ABSTRACT. ***Objective.*** To explore whether morphological features of fat infiltration (FI) on sacroiliac joint (SIJ) magnetic resonance imaging (MRI) contribute to diagnostic utility in 2 inception cohorts of patients with nonradiographic axial spondyloarthritis (nr-axSpA).

Methods. Four blinded readers assessed SIJ MRI in 2 cohorts (A/B) of 157 consecutive patients with back pain who were ≤ 50 years old, and in 20 healthy controls. Patients were classified according to clinical examination and pelvic radiography as having nr-axSpA (n = 51), ankylosing spondylitis (n = 34), or nonspecific back pain (n = 72). Readers recorded FI, bone marrow edema (BME), and erosion, predefined morphological features of FI (distinct border, homogeneity, subchondral location), and anatomical distribution of SIJ FI. The proportion of SIJ quadrants affected by FI and frequencies of various SIJ FI features were analyzed descriptively. We calculated positive/negative likelihood ratios (LR) to estimate the diagnostic utility of various features of FI, with and without associated BME, and erosion.

Results. Of the patients with nr-axSpA in cohorts A/B, 45.0%/48.4% had FI in ≥ 2 SIJ quadrants. Of those, 25.0%/22.6% and 20.0%/25.8% showed FI with distinct border or homogeneous pattern, respectively, and 50% to 100% of those patients displayed concomitant BME or erosion. FI *per se* in ≥ 2 SIJ quadrants had no diagnostic utility (LR+ 1.62/1.91). FI with distinct border (LR+ 8.29/2.13) or homogeneity (LR+ 6.24/3.78) demonstrated small to moderate diagnostic utility.

Conclusion. SIJ FI *per se* was not of clinical utility in recognition of nr-axSpA. Distinct border or homogeneity of FI on SIJ MRI showed small to moderate diagnostic utility in nr-axSpA, but were strongly associated with concomitant BME or erosion, highlighting the contextual interpretation of SIJ MRI. (First Release Dec 1 2013; J Rheumatol 2014;41:75–83; doi:10.3899/jrheum.130568)

Key Indexing Terms:
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Fat infiltration (FI) of bone marrow may be observed on T1-weighted magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) in healthy individuals (Figure 1) and in patients with mechanical back pain or spondyloarthritis (SpA). This observation has been highlighted in early reports on the use of MRI to assess the SIJ[1,2]. But it remains unclear whether selected MRI features of FI allow characterization of this lesion as pathological rather than physiological. Moreover, it is not known whether these features have diagnostic utility in early SpA.

The goal of our study was to explore whether MRI features of FI contribute to the diagnostic utility of SIJ MRI in 2 inception cohorts, which were recruited under 2 different clinical strategies to identify patients with nonradiographic axial SpA (nr-axSpA). MRI features of FI were selected by readers with extensive experience with assessment of MRI in patients with SpA and included the presence of a distinct border to the FI, homogeneity of fat signal on T1-weighted MRI, and proximity of FI to subchondral bone. Other relevant features of FI may be its association with other MRI lesions such as bone marrow

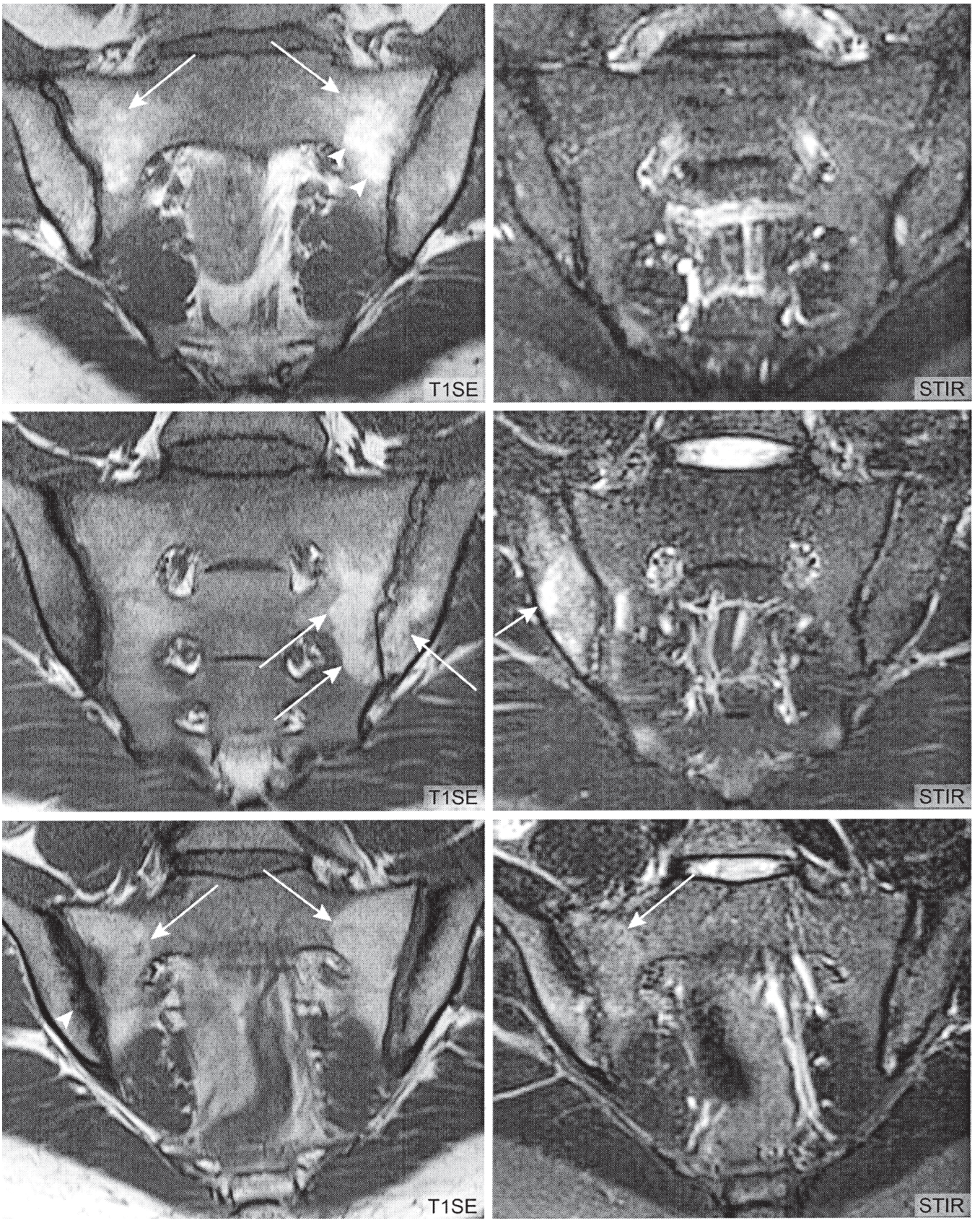

Figure 1. In each row, the left image is the T1-SE sequence and the right image is short-tau inversion recovery (STIR) sequence. Top row: Healthy control. The sacrum of a 44-year-old male healthy control displays fat infiltration (FI) on both sides (arrows). The fatty lesions show a patchy pattern and fluffy borders except for a slightly more distinct lower margin on the left side (arrowheads). The STIR sequence is normal. Middle row: Nonradiographic axial spondyloarthritis (nr-axSpA). A 35-year-old HLA-B27–positive male patient with nr-axSpA and inflammatory back pain for 11 months. The FI in the left distal sacroiliac joint (SIJ; arrows on T1-SE sequence) is characterized by a homogeneous pattern, distinct border and close proximity to the joint space. The STIR sequence shows concomitant bone marrow edema in the right SIJ (arrow). Bottom row: Ankylosing spondylitis (AS). A 26-year-old HLA-B27–positive female patient with AS and inflammatory back pain for 3 years. Bilateral extended homogeneous FI with sharp border shows along the entire joint space in both SIJ (arrows on the T1-SE sequence). The arrowhead points to one of several erosions on the right iliac side. The STIR sequence displays a faint rim bone marrow edema around the right sacral FI (arrow).

edema (BME) or erosion, and its anatomical location within the SIJ (iliac or sacral joint portion, upper or lower joint halves).

MATERIALS AND METHODS

Subjects. Two inception cohorts of consecutive patients with back pain aged ≤ 50 years were recruited in 2 university rheumatology outpatient clinics. Patients with back pain in cohort A (n = 69) were referred by rheumatologists and primary care physicians for further evaluation of suspected SpA. Twenty age-matched healthy controls, defined by the Nordic questionnaire[3] and by the absence of clinical features indicative of SpA, were concomitantly recruited by hospital staff from the same university clinic. Patients in cohort B (n = 88) presented with acute anterior uveitis (AAU) to a university ophthalmology department. All patients with AAU who indicated past or present back pain were referred to the rheumatology clinic of the same university hospital for evaluation of SpA. Subjects of both inception cohorts had not participated in previous studies evaluating SIJ MRI in SpA.

In both inception cohorts, a classification of SpA was based on the clinical opinion of 1 local rheumatologist at each center (UW for cohort A and WPM for cohort B). Patients were classified clinically and by radiographs of the pelvis as having nr-axSpA (n = 20/31, for cohort A/B, respectively), ankylosing spondylitis (AS; n = 10/24) and nonspecific back pain (NSBP; n = 39/33). Two blinded readers at each site independently categorized pelvic radiographs according to the modified New York criteria[4]; discrepancies in radiographic assessment by the local reader pair were resolved by consensus. We used the Calin criteria to assess inflammatory back pain[5]. Both SpA cohorts were enrolled in observational protocols with structured questionnaires on SpA-related clinical features and with patient-reported outcomes. The Zurich assessment was derived from the OASIS (Outcomes in Ankylosing Spondylitis International Study) protocol[6], and the Edmonton assessment followed the SPARCC (SpondyloArthritis Research Consortium of Canada) protocol[7]. Because MRI features were the independent variables that were being assessed in this study, MRI could not be used concomitantly to classify the study subjects as SpA, to avoid circuitous reasoning[8]. Patients with ongoing or previous treatment with biologics were not enrolled in both cohorts. The study protocol was approved by the local ethics review boards, and the study participants gave written informed consent.

Evaluation of MR images. The technical measures for short-tau inversion recovery and T1-SE sequences of semicoronal MR SIJ scans performed in both institutions have been published[9]. The SIJ MRI scans were blindly assessed in random order by 4 independent readers (1 radiologist: VZ; 3 rheumatologists: SJP, UW, WPM) on electronic work stations in the institution of each reader. A customized online module served to enter the MRI scores.

The evaluation of the MRI scans followed a standardized module[10]. Three MRI lesion types (FI, BME, joint erosion) were assessed according to standardized lesion definitions and a reference SIJ MR image set developed by consensus among study investigators[9,11,12]. Presence or absence of these 3 lesions was recorded as a binary variable in each quadrant (upper and lower ilium, upper and lower sacrum) of both SIJ on all MRI slices.

The following morphological features of FI on T1-SE sequence were assessed in a binary mode (Figure 1): presence or absence of a distinct border around the region of FI, homogeneity of the increased T1-weighted signal within the fat lesion, and proximity of FI to subchondral bone of the SIJ. The association of marrow FI with other SIJ lesions (BME, erosion) was evaluated on an individual level by using the detailed scoring module based on SIJ quadrants.

Statistical analysis. Differences between cohort A and B in demographic and clinical characteristics were assessed by Fisher's exact test for nominal and Wilcoxon test for continuous variables. In all analyses, a p value ≤ 0.05 was considered significant. We calculated the median proportion of SIJ quadrants affected by FI per subject over all 4 readers. We also computed this proportion separately for the sacral and iliac joint portions and for the upper and lower halves of the SIJ. The frequency of various features of FI (*per se* or in combination with BME or erosion) in patients and controls was analyzed descriptively as recorded concordantly by ≥ 2/4 readers and expressed as number of subjects (percentage). Features of FI that were assessed were FI *per se* (in ≥ 1 SIJ quadrant, and in ≥ 2 SIJ quadrants on the same slice or in ≥ 1 SIJ quadrant on ≥ 2 consecutive slices), FI with additional lesions (BME or erosion), morphological features of FI (FI with distinct border, homogeneous FI, subchondral FI, FI showing ≥ 1 or ≥ 2 morphological features), and the anatomical distribution of FI (≥ 1 quadrant with FI in all 4 sacral/iliac and upper/lower quadrants, respectively).

Intraclass correlation coefficients (ICC) for the number of affected SIJ quadrants served to calculate the reproducibility of FI among the 4 readers. Among the 6 variants of ICC, we report the results of the ICC(3,1) model, which considers the MRI readers to be a fixed sample and thus not representative of a larger population of raters[13,14]. ICC values > 0.4, > 0.6, > 0.8, and > 0.9 were regarded as representing moderate, good, very good, and excellent reproducibility, respectively. Interobserver agreement for morphological features of SIJ FI was analyzed by the mean of the pairwise estimated Cohen's κ values[15] for the 6 possible reader pairs. The interreader agreement was defined as slight, fair, moderate, substantial, and almost perfect by values of the estimated Cohen's $\kappa < 0.2$, $0.2 \le \kappa < 0.4$, $0.4 \le \kappa < 0.6$, $0.6 \le \kappa < 0.8$, and $0.8 \le \kappa < 1$, respectively[16].

The diagnostic utility of the various features of SIJ FI described above was determined by calculating the mean sensitivity, mean specificity, and positive and negative likelihood ratios (LR+, LR–) of the 4 readers and for cohort A and B. We compared the nr-axSpA and the AS group versus NSBP controls, and in cohort A additionally versus the combined group NSBP and healthy controls. The LR indicates by how much the pre-test probability is multiplied to receive the posttest probability and is based on pretest probability and the test result. The LR is independent of the prevalence of the disorder under observation[17]. According to Jaeschke[18], the clinical utility was defined as substantial, moderate, small, and poor, and rarely clinically relevant by values of LR+/LR– of > 10/< 0.1, > 5–10/0.1–0.2, > 2–5/> 0.2–0.5, and > 1–2/> 0.5–1.

RESULTS

Descriptive analysis. Demographic and clinical characteristics of the 2 SpA inception cohorts are summarized in Table 1. The different clinical recruitment strategies to

Table 1. Demographic and clinical characteristics of 2 spondyloarthritis (SpA) inception cohorts and median percentage of sacroiliac joint (SIJ) quadrants affected by fat infiltration, as recorded by 4 readers. Values for patient characteristics are the median (IQR) unless otherwise indicated.

Cohort	Cohort A (BP; n = 89)				Cohort B (AAU + BP; n = 88)		
	nr-axSpA	AS	NSBP	HC	nr-axSpA	AS	NSBP
No. subjects	20	10	39	20	31	24	33
Male:Female (% male)	11:9 (55.0)	8:2 (80.0)	11:28 (28.2)	7:13 (35.0)	17:14 (54.8)	11:13 (45.8)	17:16 (51.5)
Age, yrs	32.2 (12.3)	*30.0 (9.5)	32.7 (11.5)	30.6 (6.5)	36.2 (12.1)	*41.5 (7.1)	33.6 (15.7)
Symptom duration, yrs	*1.3 (1.8)	*3.9 (1.8)	NA	NA	*10.0 (14.0)	*12.5 (13.5)	NA
HLA-B27 positive (%)	12 (60.0)	9 (90.0)	ND[3]	ND[3]	24 (80.0)[2]	21 (87.5)	10 (55.6)[2]
BASDAI (NRS)	4.4 (3.1)[1]	5.4 (1.5)[1]	NA	NA	3.5 (4.4)	2.0 (3.4)[2]	NA
BASFI (NRS)	*1.8 (3.9)[1]	2.7 (1.5)[1]	NA	NA	*0.8 (2.3)	0.6 (2.8)[2]	NA
CRP (mg/l)	4.0 (4.5)[1]	5.0 (8.0)[1]	ND[3]	ND[3]	2.7 (5.2)	8.0 (8.7)[2]	0.9 (0.9)[2]
Percentage of SIJ quadrants with FI: median (IQR)[4]							
Per subject	4 (14)	32 (13)	1 (7)	0 (2)	7 (22)	33 (35)	0 (8)
Per sacrum R + L	4 (17)	29 (12)	0 (7)	0 (2)	2 (30)	38 (37)	0 (9)
Per ilium R + L	5 (8)	29 (17)	0 (7)	0 (0)	7 (28)	32 (38)	0 (5)
Per upper SIJ halves R + L	4 (16)	35 (12)	1 (6)	0 (4)	5 (18)	32 (36)	0 (8)
Per lower SIJ halves R + L	4 (13)	28 (11)	0 (9)	0 (2)	4 (29)	34 (38)	0 (8)

* p-value ≤ 0.05 (Fisher's exact test) between cohort A and B. [1] CRP values are based on 18, and BASDAI/BASFI values on 19 patients with nr-axSpA, respectively; BASDAI, BASFI, and CRP values are based on 9 patients with AS. [2] HLA-B27 data are based on 30 patients with nr-axSpA; BASDAI, BASFI, and CRP values are based on 22 patients with AS; in NSBP patients, HLA-B27 and CRP values are based on 18 patients; the prevalence of HLA B27 in AAU patients in general is 50–60%[31]. [3] The reason for not performing laboratory values in NSBP patients and in HC of cohort A is stated in the discussion section. [4] Percentage of SIJ quadrants with FI versus all SIJ quadrants being assessed, expressed per subject, per R and L sacrum, per R and L ilium, and per upper and lower halves of the SIJ, respectively; values are medians (IQR) over all 4 readers; $p < 0.0001$ between the groups of each cohort. AAU: acute anterior uveitis; AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BP: back pain; CRP: C-reactive protein (reference range ≤ 5 mg/l); FI: fat infiltration; HC: healthy control; L: left; NA: not applicable; ND: not done; NRS: numeric rating scale; nr-axSpA: nonradiographic axial spondyloarthritis; NSBP: nonspecific back pain; R: right.

identify patients with nr-axSpA resulted in significant differences between the 2 cohorts with cohort B (AAU plus back pain) having longer disease duration and less severe disease. Patients in cohort B with AS were older than in cohort A (median 41.5 vs 30.0 yrs, $p = 0.005$), and median symptom duration in cohort B was substantially longer, for both nr-axSpA (10.0 vs 1.3 yrs, $p < 0.0001$) and AS groups (12.5 vs 3.9 yrs, $p = 0.0002$), respectively. Patients in cohort B with nr-axSpA had less severe disease, with a significantly lower Bath Ankylosing Spondylitis Functional Index[19] (BASFI; median BASFI 0.8 vs 1.8, $p = 0.03$). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[20] values were lower in cohort B as well without reaching statistical significance. NSBP controls in cohorts A and B had a comparable median age of 32.7 and 33.6 years, respectively, close to the median age of 32.2 and 36.2 years of the corresponding nr-axSpA groups.

The median percentage of SIJ quadrants affected by FI in relation to all SIJ quadrants scored per subject was 4% and 7% for the nr-axSpA groups of cohorts A and B, respectively (Table 1). In AS, the median percentage of SIJ quadrants with FI for cohorts A and B was very similar (32% vs 33%). For cohorts A/B, the percentage of subjects showing FI in ≥ 1 SIJ quadrant as recorded by ≥ 2 readers was 55.0%/51.6% in nr-axSpA, 90.0%/100.0% in AS, and 38.5%/27.3% in NSBP, respectively, and 20.0% of the healthy controls in cohort A (Table 2). These proportions changed little when FI was alternatively defined as ≥ 2 SIJ quadrants with FI on 1 slice or ≥ 1 SIJ quadrant showing FI on ≥ 2 consecutive slices (Table 2).

Mean ICC (range) for the number of SIJ quadrants showing FI for the 6 reader pairs were 0.59 (0.39–0.83) and 0.75 (0.61–0.86) for cohorts A and B, respectively. For cohorts A/B, the mean κ values (range) for the 6 reader pairs were 0.58 (0.44–0.75)/0.57 (0.51–0.65) for FI with distinct border, 0.53 (0.44–0.73)/0.59 (0.48–0.69) for homogeneous FI, and 0.38 (0.12–0.56)/0.50 (0.35–0.68) for subchondral FI.

Isolated SIJ FI was rare in nr-axSpA and AS groups in both cohorts (0%/6.5% in nr-axSpA and 0%/8.3% in AS for cohorts A/B, respectively; Table 2). NSBP controls showed a higher frequency of isolated SIJ FI (23.1%/9.1%). In cohorts A/B, FI associated with BME was reported in 72.7%/56.3% (nr-axSpA) and 88.9%/87.5% (AS) of those subjects showing FI in ≥ 1 SIJ quadrant as recorded by ≥ 2 readers. The same proportions for FI associated with erosion were 54.5%/62.5% for nr-axSpA and 100.0%/87.5% for AS in cohort A/B, respectively.

For nr-axSpA and cohorts A/B, FI with distinct border was reported in 45.5%/43.8% of those subjects showing FI in ≥ 1 SIJ quadrant as recorded by ≥ 2 readers (Table 2). The proportion of FI with distinct border associated with BME was 80.0%/57.1% and associated with erosion 60.0%/100.0%. Homogeneous FI was recorded in 36.4%/50.0% of patients with nr-axSpA having FI in ≥ 1 SIJ quadrant and they showed an association with BME in 75.0%/62.5% and with erosion in 50.0%/87.5% for cohorts A/B. Subchondral FI

Table 2. Frequency of fat infiltration as recorded by ≥ 2 readers. Data are no. subjects (percentage).

Cohort	Cohort A (BP; n = 89)				Cohort B (AAU + BP; n = 88)		
Group	nr-axSpA	AS	NSBP	HC	nr-axSpA	AS	NSBP
No. subjects	20	10	39	20	31	24	33
FI per se							
FI in ≥ 1 SIJ quadrant	11 (55.0)	9 (90.0)	15 (38.5)	4 (20.0)	16 (51.6)	24 (100.0)	9 (27.3)
FI in ≥ 2 SIJ quadrants[1]	9 (45.0)	9 (90.0)	14 (35.9)	2 (10.0)	15 (48.4)	24 (100.0)	8 (24.2)
FI with additional MRI lesions							
Fat w/o BME or erosion	0 (0)	0 (0)	9 (23.1)	1 (5.0)	2 (6.5)	2 (8.3)	3 (9.1)
FI w/BME	8 (40.0)	8 (80.0)	5 (12.8)	2 (10.0)	9 (29.0)	21 (87.5)	5 (15.2)
FI w/erosion	6 (30.0)	9 (90.0)	0 (0)	0 (0)	10 (32.3)	21 (87.5)	3 (9.1)
Morphological features of FI							
FI w/distinct border	5 (25.0)	6 (60.0)	1 (2.6)	0 (0)	7 (22.6)	16 (66.7)	3 (9.1)
FI w/distinct border + BME	4 (20.0)	5 (50.0)	1 (2.6)	0 (0)	4 (12.9)	10 (41.7)	3 (9.1)
FI w/distinct border + erosion	3 (15.0)	6 (60.0)	0 (0)	0 (0)	7 (22.6)	13 (54.2)	3 (9.1)
Homogeneous FI	4 (20.0)	6 (60.0)	0 (0)	0 (0)	8 (25.8)	18 (75.0)	3 (9.1)
Homogeneous FI + BME	3 (15.0)	5 (50.0)	0 (0)	0 (0)	5 (16.1)	12 (50.0)	3 (9.1)
Homogeneous FI + erosion	2 (10.0)	6 (60.0)	0 (0)	0 (0)	7 (22.6)	14 (58.3)	3 (9.1)
Subchondral FI	7 (35.0)	8 (80.0)	7 (17.9)	1 (5.0)	12 (38.7)	24 (100.0)	5 (15.2)
Subchondral FI + BME	5 (25.0)	7 (70.0)	2 (5.1)	0 (0)	9 (29.0)	21 (87.5)	5 (15.2)
Subchondral FI + erosion	5 (25.0)	8 (80.0)	0 (0)	0 (0)	10 (32.3)	21 (87.5)	4 (12.1)
FI with ≥ 1 feature[2]	7 (35.0)	9 (90.0)	8 (20.5)	1 (5.0)	12 (38.7)	24 (100.0)	6 (18.2)
FI with ≥ 1 feature + BME	5 (25.0)	8 (80.0)	3 (7.7)	1 (5.0)	9 (29.0)	21 (87.5)	5 (15.2)
FI with ≥ 1 feature + erosion	5 (25.0)	9 (90.0)	0 (0)	0 (0)	10 (32.3)	21 (87.5)	4 (12.1)
FI with ≥ 2 features[2]	5 (25.0)	6 (60.0)	1 (2.6)	0 (0)	11 (35.5)	18 (75.0)	3 (9.1)
FI with ≥ 2 features + BME	4 (20.0)	5 (50.0)	1 (2.6)	0 (0)	8 (25.8)	13 (54.2)	3 (9.1)
FI with ≥ 2 features + erosion	3 (15.0)	6 (60.0)	0 (0)	0 (0)	9 (29.0)	15 (62.5)	3 (9.1)
Anatomical distribution of FI							
≥ 1 FI in all 4 sacral quadrants	5 (25.0)	7 (70.0)	6 (15.4)	2 (10.0)	6 (19.4)	19 (79.2)	2 (6.1)
≥ 1 FI in all 4 iliac quadrants	0 (0)	5 (50.0)	3 (7.7)	0 (0)	4 (12.9)	14 (58.3)	1 (3.0)
≥ 1 FI in all 4 upper quadrants	0 (0)	6 (60.0)	4 (10.3)	1 (5.0)	6 (19.4)	14 (58.3)	0 (0)
≥ 1 FI in all 4 lower quadrants	1 (5.0)	6 (60.0)	3 (7.7)	0 (0)	9 (29.0)	17 (70.8)	2 (6.1)

[1] FI in ≥ 2 SIJ quadrants on the same slice or in ≥ 1 SIJ quadrant on ≥ 2 adjacent slices. [2] Morphological features of FI: FI with distinct border, homogeneous FI, subchondral FI. AAU: acute anterior uveitis; AS: ankylosing spondylitis; BME: bone marrow edema; BP: back pain; FI: fat infiltration; HC: healthy control; MRI: magnetic resonance imaging; nr-axSpA: nonradiographic axial spondyloarthritis; NSBP: nonspecific back pain; SIJ: sacroiliac joint.

was seen in 63.6%/75.0% of nr-axSpA patients with FI in ≥ 1 SIJ quadrant, associated with BME in 71.4%/75.0% and with erosion in 71.4%/83.3%. In NSBP controls, subchondral FI was seen more frequently (17.9%/15.2%) than FI with distinct border (2.6%/9.1%) or homogeneity (0%/9.1%). Of the subjects showing a distinct border to FI, 89.5% also had homogeneous FI. The association of subchondral SIJ FI with distinct border or with homogeneous FI was 100% each.

For cohorts A/B, at least 1 fat lesion in all 4 sacral quadrants was reported in 25.0%/19.4% of nr-axSpA and in 70.0%/79.2% of patients with AS (Table 2). The same proportions for at least 1 fat lesion in all 4 iliac quadrants were 0%/12.9% and 50.0%/58.3% for nr-axSpA and AS groups, respectively.

Regarding the diagnostic utility of SIJ FI in nr-axSpA versus NSBP patients, FI *per se* expressed as FI in ≥ 1 SIJ quadrant (LR+ 1.64/1.92) or as FI without associated BME or erosion (LR+ 0.28/0.87) had no diagnostic utility in cohorts A/B (Table 3). FI associated with BME had poor to small diagnostic utility (LR+ 4.32/1.85) for cohorts A/B; for FI associated with erosion, diagnostic utility was high in cohort A (LR+ 17.55) and small in cohort B (LR+ 2.43). FI with distinct border (LR+ 8.29/2.13) and homogeneous FI (LR+ 6.24/3.78) showed a small to moderate diagnostic utility in cohorts A/B; their association with BME increased diagnostic utility in cohort A, and diagnostic utility increased with erosion in both cohorts. Subchondral FI had a small diagnostic utility (LR+ 2.36/2.04). FI with any 2 morphological features had a small to borderline substantial diagnostic utility (LR+ 9.26/3.58). The 4 variants of anatomical distribution of FI had a poor to small diagnostic utility.

Regarding the diagnostic utility of SIJ FI in AS versus NSBP patients, FI *per se* had poor to small diagnostic utility in cohorts A/B (LR+ for FI in ≥1 SIJ quadrant 2.48/3.51, FI without BME or erosion 0.14/0.88; Table 4). The higher diagnostic utility for FI associated with BME or erosion, for morphological features of FI, and for the anatomical distribution of FI in the AS group compared with the nr-axSpA

Table 3. Diagnostic utility of fat infiltration of the SIJ in nr-axSpA versus NSBP patients: mean sensitivity and specificity over 4 readers for cohort A/B (in parentheses for cohort A: nr-axSpA vs NSBP and HC combined).

Variable	Sensitivity	Specificity	Positive LR	Negative LR
FI per se				
FI in ≥ 1 SIJ quadrant	0.46 (0.46)/0.44	0.72 (0.74)/0.77	1.64 (1.79)/1.92	0.75 (0.72)/0.73
FI in ≥ 2 SIJ quadrants[1]	0.44 (0.44)/0.42	0.73 (0.77)/0.78	1.62 (1.91)/1.91	0.77 (0.73)/0.74
FI with additional MRI lesions				
FI w/o BME or erosion	0.05 (0.05)/0.07	0.82 (0.84)/0.92	0.28 (0.31)/0.87	1.16 (1.13)/1.01
FI w/BME	0.39 (0.39)/0.27	0.91 (0.91)/0.86	4.32 (4.35)/1.85	0.67(0.67)/0.86
FI w/erosion	0.34 (0.34)/0.26	0.98 (0.99)/0.89	17.55 (26.55)/2.43	0.68 (0.67)/0.83
Morphological features of FI				
FI w/distinct border	0.21 (0.21)/0.21	0.97 (0.98)/0.90	8.29 (12.54)/2.13	0.81 (0.80)/0.88
FI w/distinct border + BME	0.20 (0.20)/0.12	0.99 (0.99)/0.91	15.60 (23.60)/1.33	0.81 (0.81)/0.97
FI w/distinct border + erosion	0.18 (0.18)/0.19	1.00 (1.00)/0.95	NC (NC)/3.50	0.82 (0.82)/0.86
Homogeneous FI	0.20 (0.20)/0.26	0.97 (0.97)/0.93	6.24 (7.87)/3.78	0.83 (0.82)/0.80
Homogeneous FI + BME	0.19 (0.19)/0.16	0.99 (0.99)/0.93	14.63 (14.75)/2.37	0.82 (0.82)/0.90
Homogeneous FI + erosion	0.15 (0.15)/0.19	1.00 (1.00)/0.95	NC (NC)/3.50	0.85 (0.85)/0.86
Subchondral FI	0.36 (0.36)/0.35	0.85 (0.86)/0.83	2.36 (2.59)/2.04	0.75 (0.74)/0.78
Subchondral FI + BME	0.31 (0.31)/0.24	0.94 (0.94)/0.86	4.88 (5.27)/1.77	0.73 (0.73)/0.88
Subchondral FI + erosion	0.26 (0.26)/0.25	0.99 (0.99)/0.89	20.48 (30.98)/2.36	0.75 (0.74)/0.84
FI with ≥ 1 feature[2]	0.36 (0.36)/0.35	0.83 (0.84)/0.81	2.09 (2.31)/1.87	0.77 (0.76)/0.80
FI with ≥ 1 feature + BME	0.31 (0.31)/0.24	0.93 (0.93)/0.86	4.43 (4.61)/1.68	0.74 (0.74)/0.89
FI with ≥ 1 feature + erosion	0.26 (0.26)/0.25	0.99 (0.99)/0.89	20.48 (30.98)/2.36	0.75 (0.74)/0.84
FI with ≥ 2 features[2]	0.24 (0.24)/0.30	0.97 (0.98)/0.92	9.26 (14.01)/3.58	0.78 (0.78)/0.77
FI with ≥ 2 features + BME	0.23 (0.23)/0.19	0.99 (0.99)/0.92	17.55 (26.55)/2.32	0.79 (0.78)/0.88
FI with ≥ 2 features + erosion	0.19 (0.19)/0.23	1.00 (1.00)/0.95	NC (NC)/4.26	0.81 (0.81)/0.82
Anatomical distribution of FI				
≥ 1 FI in all 4 sacral quadrants	0.18 (0.18)/0.19	0.90 (0.91)/0.92	1.71 (1.88)/2.23	0.92 (0.91)/0.89
≥ 1 FI in all 4 iliac quadrants	0.04 (0.04)/0.10	0.95 (0.96)/0.95	0.73 (0.98)/1.82	1.01 (1.00)/0.95
≥ 1 FI in all 4 upper quadrants	0.06 (0.06)/0.12	0.94 (0.95)/0.96	1.08 (1.34)/3.19	0.99 (0.98)/0.91
≥ 1 FI in all 4 lower quadrants	0.06 (0.06)/0.22	0.93 (0.95)/0.94	0.89 (1.23)/3.59	1.01 (0.99)/0.83

Differences in positive or negative LR despite identical mean sensitivity and specificity data result from rounding differences. [1] FI in ≥ 2 SIJ quadrants on the same slice or in ≥ 1 SIJ quadrant on ≥ 2 adjacent slices. [2] Morphological features of FI: FI with distinct border, homogeneous FI, subchondral FI. BME: bone marrow edema; FI: fat infiltration; HC: healthy control; LR: likelihood ratio; MRI: magnetic resonance imaging; NC: not calculable; nr-axSpA: non-radiographic axial spondyloarthritis; NSBP: nonspecific back pain; SIJ: sacroiliac joint; SpA: spondyloarthritis.

group is attributable to an overall higher sensitivity with unchanged specificity, which reflects the higher prevalence of SIJ FI in the AS group.

DISCUSSION

This cross-sectional analysis of SIJ MRI in 2 SpA inception cohorts explored the diagnostic utility of several features of FI in nr-axSpA. FI *per se* was not useful in recognition of SpA. SIJ FI characterized by a distinct border or homogeneity on MRI had small to moderate diagnostic utility in nr-axSpA. However, 50% to 100% of patients with nr-axSpA having 1 of these 2 morphological features of FI concomitantly showed BME or erosion on SIJ MRI, which emphasizes the mutual effect and contextual relevance of concomitant MRI features for a diagnosis of SpA. The anatomical fat distribution according to sacral/iliac joint portion or upper/lower joint halves did not facilitate recognition of nr-axSpA.

FI in the SIJ was detected in fewer SIJ quadrants in nr-axSpA than in patients with AS. A possible explanation is the hypothesis that FI may accumulate over time and follow resolution of SIJ inflammation. The MRI findings of a recently published interventional trial with etanercept versus sulfasalazine in axial SpA over 48 weeks support a relationship between BME and subsequent development of FI in the subchondral bone of the SIJ[21]. The authors found a significant relationship between resolution of baseline SIJ BME upon treatment and the appearance of new FI in 10.5% of SIJ quadrants at Week 48. With persisting BME, only 2.4% of SIJ quadrants showed new fatty lesions at followup. The mean percentage of 38.8% SIJ quadrants affected by FI in 65 patients with axial SpA (50.8% meeting the modified New York criteria) compares well to our median proportion of SIJ quadrants showing FI in 32%/33% of patients with AS for cohorts A/B. An observational study from Denmark found a significant relationship as well between baseline SIJ activity and progression of SIJ FI over 2-7 years in 94 patients with axial SpA without treatment with tumor necrosis factor-α inhibitors[22]. A small retrospective study found an association between subchondral SIJ FI and higher SIJ scores on pelvic radiographs[23]. However, there are no longitudinal data regarding a possible increase of fat infil-

Table 4. Diagnostic utility of fat infiltration of the SIJ in AS versus NSBP patients: mean sensitivity and specificity over 4 readers for cohort A/B (in parentheses for cohort A: AS vs NSBP and HC combined).

Variable	Sensitivity	Specificity	Positive LR	Negative LR
FI per se				
FI in ≥ 1 SIJ quadrant	0.70 (0.70)/0.80	0.72 (0.74)/0.77	2.48 (2.71)/3.51	0.42 (0.40)/0.26
FI in ≥ 2 SIJ quadrants[1]	0.70 (0.70)/0.80	0.73 (0.77)/0.78	2.60 (3.06)/3.63	0.41 (0.39)/0.26
FI with additional MRI lesions				
FI w/o BME or erosion	0.03 (0.03)/0.07	0.82 (0.84)/0.92	0.14 (0.16)/0.88	1.19 (1.16)/1.01
FI w/BME	0.58 (0.58)/0.61	0.91 (0.91)/0.86	6.41 (6.46)/4.22	0.47 (0.47)/0.46
FI w/erosion	0.68 (0.68)/0.67	0.98 (0.99)/0.89	35.10 (53.10)/6.31	0.33 (0.33)/0.37
Morphological features of FI				
FI w/distinct border	0.53 (0.53)/0.49	0.97 (0.98)/0.90	20.47 (30.98)/5.02	0.49 (0.48)/0.56
FI w/distinct border + BME	0.40 (0.40)/0.36	0.99 (0.99)/0.91	31.20 (47.20)/3.92	0.61 (0.61)/0.71
FI w/distinct border + erosion	0.50 (0.50)/0.40	1.00 (1.00)/0.95	NC (NC)/7.61	0.50 (0.50)/0.63
Homogeneous FI	0.58 (0.58)/0.58	0.97 (0.97)/0.93	17.94 (22.62)/8.48	0.44 (0.44)/0.45
Homogeneous FI + BME	0.45 (0.45)/0.42	0.99 (0.99)/0.93	35.10 (35.40)/6.14	0.56 (0.56)/0.62
Homogeneous FI + erosion	0.55 (0.55)/0.46	1.00 (1.00)/0.95	NC (NC)/8.75	0.45 (0.45)/0.57
Subchondral FI	0.70 (0.70)/0.75	0.85 (0.86)/0.83	4.55 (5.01)/4.33	0.35 (0.35)/0.30
Subchondral FI + BME	0.58 (0.58)/0.58	0.94 (0.94)/0.86	8.97 (9.69)/4.22	0.45 (0.45)/0.49
Subchondral FI + erosion	0.68 (0.68)/0.64	0.99 (0.99)/0.89	52.65 (79.65)/6.01	0.33 (0.33)/0.41
FI with ≥ 1 feature[2]	0.73 (0.73)/0.75	0.83 (0.84)/0.81	4.19 (4.62)/3.99	0.33 (0.33)/0.30
FI with ≥ 1 feature + BME	0.60 (0.60)/0.58	0.93 (0.93)/0.86	8.51 (8.85)/4.00	0.43 (0.43)/0.50
FI with ≥ 1 feature + erosion	0.70 (0.70)/0.64	0.99 (0.99)/0.89	54.60 (82.60)/6.01	0.30 (0.30)/0.41
FI with ≥ 2 features[2]	0.58 (0.58)/0.59	0.97 (0.98)/0.92	22.42 (33.93)/7.06	0.44 (0.43)/0.45
FI with ≥ 2 features + BME	0.45 (0.45)/0.43	0.99 (0.99)/0.92	35.10 (53.10)/5.15	0.56 (0.55)/0.62
FI with ≥ 2 features + erosion	0.55 (0.55)/0.47	1.00 (1.00)/0.95	NC (NC)/8.94	0.45 (0.45)/0.56
Anatomical distribution of FI				
≥ 1 FI in all 4 sacral quadrants	0.45 (0.45)/0.58	0.90 (0.91)/0.92	4.39 (4.83)/6.91	0.61 (0.61)/0.46
≥ 1 FI in all 4 iliac quadrants	0.35 (0.35)/0.42	0.95 (0.96)/0.95	6.82 (9.18)/7.89	0.69 (0.68)/0.61
≥ 1 FI in all 4 upper SIJ quadrants	0.43 (0.43)/0.42	0.94 (0.95)/0.96	7.37 (9.12)/11.04	0.61 (0.60)/0.60
≥ 1 FI in all 4 lower SIJ quadrants	0.43 (0.43)/0.57	0.93 (0.95)/0.94	6.03 (8.36)/9.33	0.62 (0.61)/0.46

Differences in positive or negative LR despite identical mean sensitivity and specificity data result from rounding differences. [1] FI in ≥ 2 SIJ quadrants on the same slice or in ≥ 1 SIJ quadrant on ≥ 2 adjacent slices. [2] Morphological features of FI: FI with distinct border, homogeneous FI, subchondral FI. AS: ankylosing spondylitis; BME: bone marrow edema; FI: fat infiltration; HC: healthy control; LR: likelihood ratio; MRI: magnetic resonance imaging; NC: not calculable; NSBP: nonspecific back pain; SIJ: sacroiliac joint; SpA: spondyloarthritis.

tration in the SIJ over time in NSBP and healthy controls. FI in ≥ 2 SIJ quadrants was observed in 10% to 36% of NSBP and healthy controls, but less than 10% of the controls also showed a distinct border or homogeneity of FI. The clinical relevance of SIJ FI in NSBP and healthy controls remains unclear.

The diagnostic utility of SIJ FI characterized by a distinct border or homogeneity on MRI was small to moderate in nr-axSpA and moderate to substantial in AS. However, 50% to 100% of patients with nr-axSpA and 57% to 100% of patients with AS having 1 of these 2 morphological features of FI concomitantly showed BME or erosion on SIJ MRI. It is not possible to disentangle the mutual effect of fat morphology features and associated SIJ MRI lesions, such as BME or erosion. This contextual interpretation of different MRI features observed concomitantly in the same SIJ MRI may be relevant for global assessment of the scan. Assessment of fat lesions in the SIJ may enhance diagnostic interpretation of SIJ MRI in some early SpA patients with equivocal erosion or BME, where FI with distinct border or homogeneous pattern may enhance confidence in a diagnosis of nr-axSpA. On the other hand, obvious BME or erosion may affect the interpretation of morphological features of fat infiltration on SIJ MRI. However, formal proof of this hypothesis of an incremental value of concomitant lesions on SIJ MRI cannot be obtained, as lesions tend to occur simultaneously on the same scan. It is technically impossible to remove this source of reader bias.

The proportions of SIJ quadrants affected by FI and of morphological features, and the diagnostic utility of FI *per se* were comparable between the nr-axSpA, AS, and NSBP groups of the 2 cohorts. Variations in sensitivity, specificity, and LR+/LR– between the groups of the 2 cohorts for the other features of FI may be explained by different modes of recruitment of patients with suspected nr-axSpA in the 2 cohorts and differences in demographic and clinical characteristics between cohorts A and B. Patients of cohort A with back pain were referred by rheumatologists and primary care physicians to a tertiary care center for evaluation of suspected SpA and had higher disease activity by BASFI and BASDAI than patients in cohort B. Patients in cohort B were recruited by a tertiary ophthalmology department for

AAU and referred for rheumatologic evaluation if they additionally indicated present or past back pain. Long symptom duration as observed in cohort B has been described in several recent reports in patients with nr-axSpA. Two interventional trials in patients with nr-axSpA reported a symptom duration of 7-8 years and 10.1 years, respectively[24,25], and a recent cross-sectional analysis showed that 61.4% of 44 patients with nr-axSpA had a symptom duration of more than 5 years[26]. In 2 observational studies, only 33.3% and 24.3% of patients with nr-axSpA progressed to radiographic sacroiliitis over 7.7 and 10 years of followup, respectively[27,28]. A long symptom duration for nr-axSpA cohorts has been reported previously[29].

We included 2 inception cohorts of patients with back pain and showed that despite the differences in referral, the conclusions were the same. Further strengths of our study are that data were based on readers from 3 international sites and inclusive of both radiologists and rheumatologists. We also included scans from healthy controls for further methodological rigor in MRI reading. The principal limitation inherent to imaging studies in nr-axSpA is the selection of the gold standard[30]. To avoid conceptual circularity, MRI should not be used for classification when it is also being evaluated for its diagnostic utility[8]. Gold standard for classification of SpA was therefore physician expert opinion. Patients were also enrolled in standardized protocols to assess inflammatory back pain and SpA-related clinical features. HLA-B27 has limited diagnostic value in cohort B recruited by the key symptom AAU; about 50% to 60% of patients with AAU are HLA-B27 positive because of their AAU[31]. Assessment of laboratory values in controls of cohort A was not permitted by the local ethics committee owing to concerns that incidental positive findings may cause psychological harm. Patient characteristics in the study leading to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria showed a frequency of HLA-B27 positivity in the non-SpA group of 27.7%[32], a finding that reflects the screening bias of the referring physicians toward factors that increase their suspicion of SpA in subjects with chronic back pain.

The physician gold standard was the accepted endpoint for the development of the ASAS classification criteria[32], and early SpA cohorts, such as DESIR, selected the physician's expert opinion as gold standard[33]. Our approach with physician expert opinion as gold standard for an MRI study in nr-axSpA does not exclude the possibility of both false positive and false negative clinical assignments. The optimal gold standard would be reevaluation of the initial classification by longitudinal followup. However, longitudinal studies are limited by patients lost to followup, particularly in disorders with slow progression such as SpA, which requires a lengthy followup.

FI of the SIJ alone contributed little to recognition of nr-axSpA. We speculate that assessment of fat lesions in the SIJ may facilitate diagnostic interpretation of SIJ MRI in some patients with early SpA and equivocal erosion or BME, where FI with distinct border or homogeneous pattern may enhance confidence in a diagnosis of nr-axSpA. However, formal proof of an incremental value of SIJ FI is not possible because FI is often observed simultaneously with BME and/or erosion on the same SIJ scan emphasizing the contextual interpretation of concomitant lesions on MRI scans.

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