Diagnosis and classification of axial spondyloarthritis : imaging and non-imaging features

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Presence of multiple spondyloarthritis (SpA)-features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the Spondyloarthritis Caught Early (SPACE)-cohort.

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ABSTRACT

Objectives

Concerns have been raised about overdiagnosis of axial spondyloarthritis (axSpA). We investigated whether patients with chronic back pain (CBP) of short duration and multiple SpA-features are always diagnosed with axSpA by the rheumatologist, and to what extent fulfilment of the ASAS axSpA criteria is associated with an axSpA diagnosis.

Methods

Baseline data from 500 patients from the SPondyloArthritis Caught Early (SPACE)-cohort which includes CBP patients (≥ 3 months, ≤ 2 years, onset < 45 years) were analysed. All patients underwent full diagnostic work-up including MRI-SI and X-SI. For each patient, the total number of SpA-features excluding sacroiliac imaging and HLA-B27 status was calculated.

Results

Before sacroiliac imaging and HLA-B27 testing, 32% of patients had ≤1 SpA-feature, 29% had 2 SpA-features, 16% had 3 SpA-features and 24% had ≥4 SpA-features. A diagnosis of axSpA was made in 250 (50%) of the patients: 24% with ≤1 SpA-feature, 43% with 2 SpA-features, 62% with 3 SpA-features and 85% with ≥4 SpA-features. Of the 230 patients with a positive ASAS classification 40 (17.4%) did not have a diagnosis of axSpA. HLA-B27 positivity (OR 5.6; 95% CI 3.7 to 8.3) and any (MRI-SI and/or X-SI) positive imaging (OR 34.3; 95% CI 17.3 to 67.7) were strong determinants of an axSpA diagnosis

Conclusion

In this cohort of CBP patients, neither the presence of numerous SpA-features nor fulfilment of the ASAS classification criteria did automatically lead to a diagnosis axSpA. Positive imaging was considered particularly important in making a diagnosis of axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) has a heterogeneous clinical presentation and does not have a single pathognomonic feature that distinguishes the disease from other conditions with similar symptoms.[1, 2] Therefore, it is a challenge to identify axSpA early in patients with chronic back pain (CBP). In daily rheumatologic practice, a diagnosis of axSpA is generally made in patients with CBP on the basis of a combination of symptoms from medical history, physical examination, laboratory investigations, and findings on imaging.[3, 4]

In 2009 the Assessment of SpondyloArthritis international Society (ASAS) developed classification criteria for axSpA. The criteria combine information from several sources such as medical history, physical examination, laboratory testing, and imaging.[5] In a secondary or tertiary care setting the fulfilment of the ASAS-criteria is strongly associated with a clinical diagnosis of axSpA at the group level, but the criteria cannot be used for diagnosing axSpA in individual patients.[6, 7] Classification criteria can only be applied in patients in whom a diagnosis of axSpA has been established (not vice versa).[8-10] The recognition of axSpA therefore requires the physician's knowledge about SpA, as well as expertise in aggregating information obtained during the diagnostic work-up and a differential diagnosis.

In order to assist physicians in the diagnosis of axSpA the ASAS modified Berlin algorithm has been developed, which can be applied in CBP patients with age of onset <45 years (**Figure** 1). As a first step the algorithm advises a radiograph of the sacroiliac joints (X-SI) in all patients. According to the algorithm CBP patients with indisputable radiographic sacroiliitis may be readily diagnosed with axSpA. Patients without clear sacroiliitis on radiographs are subsequently stratified according to the number of spondyloarthritis (SpA)-features they have after patient history, physical examination and measuring C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). A important feature of the algorithm is that it allows a diagnosis of axSpA in patients with ≥4 SpA-features without further imaging (MRI of the sacroiliac joints (MRI-SI)) or HLA-B27 testing. Moreover, HLA-B27 positive patients with normal radiographs and 2 or 3 SpA-features may also be diagnosed with axSpA without performing MRI-SI. Van den Berg et al. have already shown that an axSpA diagnosis according to the modified Berlin algorithm is not necessarily the same as an expert's (i.e. rheumatologist's) clinical diagnosis, so false-positive and false-negative diagnoses may occur if the algorithm is followed blindly.[11] Therefore, it should be stressed again that the ASAS modified Berlin algorithm is only a tool in aiding rheumatologists in diagnosing axSpA and can and should not replace a differential diagnostic procedure in patients with CBP.

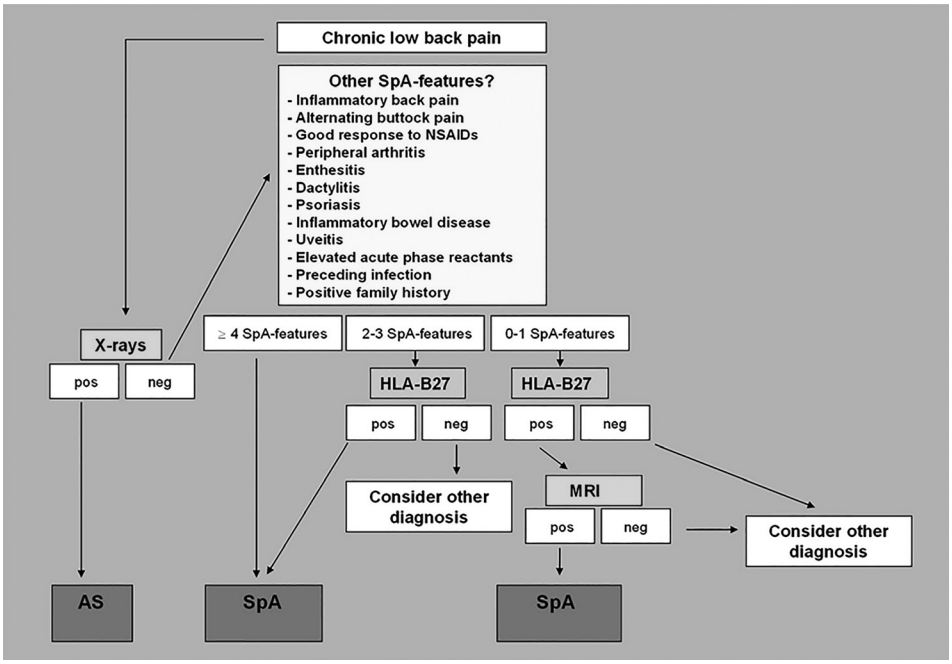

Figure 1 ASAS modification of the Berlin algorithm* for diagnosing axial spondyloarthritis. *Adapted from*: van den Berg R et al. Ann Rheum Dis 2013;72;1646-53 (with permission). *Rudwaleit M et al. Ann Rheum Dis 2004;63:535-43.

Nevertheless, several concerns have been raised about the risk of overdiagnosis of axSpA when the diagnosis is made by counting the number of SpA-features without paying attention to an alternative diagnosis that may be more likely.[12] Similarly, the use of ASAS classification as diagnostic criteria may lead to misdiagnosis. These issues are of particular concern in patients with non-inflammatory conditions in whom overdiagnosis may inappropriately lead to the start of anti-inflammatory treatments that will not be effective but are associated with side-effects and costs. Concerns like these have contributed to the United States Food and Drug Administration (FDA) formal disproval of adalimumab and certolizumab for the treatment of non-radiographic axSpA in the United States, while both drugs have been approved by the European Medicines Agency (EMA) for this indication in the European Union.[13]

The diagnostic process of early axSpA in patients presenting with CBP is not well studied. Cohort studies typically include patients with an established diagnosis of axSpA. The multicenter SPondyloArthritis Caught Early (SPACE)-cohort is a study that has included

patients presenting with CBP but without a formal diagnosis who have been referred to a rheumatologist. Consequently, the SPACE-cohort contains patients with and without a diagnosis of axSpA.

The main objectives of our study were to investigate 1) which SpA-features contribute most to a diagnosis of axSpA; 2) if the presence of multiple SpA-features automatically leads to a diagnosis of axSpA in patients presenting with CBP; and 3) how positive classification according to the ASAS-criteria relates to a diagnosis of axSpA.

METHODS

Study design and population

The SPACE-cohort is a prospective multicenter study, which was initiated in January 2009. The study has been described elsewhere.[14] In brief, patients with CBP (≥3 months and ≤ 2 years) of unknown origin and age of onset <45 years were included. Patients were recruited for the study from five different rheumatology outpatient clinics in the Netherlands (Amsterdam, Gouda, Leiden), Norway (Oslo) and Italy (Padua).

Approval for the study was obtained from all local medical ethics committees. All patients provided written informed consent. Data of 157 patients from the LUMC in Leiden have previously been published as part of the validation of the modified Berlin algorithm.

Imaging of the sacroiliac joints

Plain radiographs of the pelvis (X-SI) were performed in anteroposterior view. MRI-SI were also performed: the acquired sequences were coronal oblique T1-weighted turbo spin echo (TSE) and short tau inversion recovery (STIR) with a slice thickness of 4 mm. Each center interpreted the radiographs and MRI-SI on the presence of sacroiliitis using global assessment as part of routine clinical practice (local reading) with radiologists specifically asked whether there was evidence of sacroiliitis.

Clinical measurements

Patients underwent a full diagnostic work-up including the assessment of SpA-features according to the ASAS-criteria: CRP and ESR, HLA-B27, imaging (X-SI and MRI-SI), and the actual presence or a history of all other SpA-features: inflammatory back pain (IBP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), positive family history

of SpA, peripheral arthritis, dactylitis, enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), psoriasis. Rheumatologists provided a diagnosis of axSpA based on all collected information, including imaging and HLA-B27 status. In case of 'no axSpA' rheumatologists were asked to provide a most likely alternative diagnosis. In addition, rheumatologists were requested to provide a level of confidence about the diagnosis on a 11-point numerical rating scale (NRS) ranging from 0 (not confident at all) to 10 (very confident) after imaging was performed. Independently of the clinical diagnosis the ASAS axSpA classification criteria were used to classify patients using the local imaging results. The rheumatologists were not formally informed about the patients' classification status at the time of diagnosis.

Statistical analysis

For the present analyses baseline data were available (n=522). Patients with missing values for ≥1 SpA-feature, including imaging and HLA-B27 status, and those with missing information on clinical diagnosis, were excluded from the analyses (n=22). Total number of SpA-features was determined without taking HLA-B27 and imaging into account. Next, patients were stratified according to the number of SpA-features present: ≤1 feature, 2 features, 3 features, and ≥4 features. Patient characteristics are presented for the total patient group and for each subgroup as mean ± SD or number (%). The rheumatologist's diagnosis was the main outcome. Sensitivity and specificity were calculated to assess the agreement between the clinical diagnosis and the ASAS axSpA classification criteria. Where zeroes caused problems with computation of odds ratios or their standard errors, 0.5 were added to all cells. Multivariable logistic regression analysis was performed to assess independent determinants of clinical diagnosis. Data analysis was performed using STATA SE V.14. *P* values less than 0.05 were considered significant.

RESULTS

A total of 500 patients with CBP of short duration and complete data were analysed. Of these patients 37% were male, mean age (SD) was 29.3 (8.3) years and mean symptom duration (SD) was 13.4 (7.4) months (**Table 1**). Of all patients, 159 (32%) had ≤1 feature, 143 (29%) had 2 features, 79 (16%) had 3 features and 119 (24%) had ≥4 features. Age at onset of back pain, sex, and disease duration were similar across subgroups. Of the 159 patients in the ≤1 SpA-feature subgroup 24% was diagnosed with axSpA; for patients with 2 SpA-features this was 43%, for patients with 3 SpA-features 62%, and for patients with ≥4 SpA-features this was 85%. When stratifying for each participating center the same trend - higher percentages of diagnosis with increasing numbers of features - in clinical diagnosis was observed (supplementary data Table S1).

In patients with ≤1 SpA-feature 9/159 (6%) had radiographic sacroiliitis and 26/159 (16%) had a positive MRI-SI (**Table 2**). Of the patients with normal radiographs 99/150 (66%) had neither a positive MRI-SI nor HLA-B27 and only 2/99 (2%) were diagnosed with axSpA (both CBP patients had 1 SpA-feature which were IBP and positive family history, respectively). In total, 38/159 (24%) patients were diagnosed with axSpA. One patient with radiographic sacroiliitis was not diagnosed with axSpA. When the ASAS axSpA classification criteria were applied, 5 patients without a diagnosis of axSpA fulfilled the ASAS-criteria. In addition, 13 patients with an axSpA diagnosis did not fulfil the ASAS classification criteria.

In patients with 2 SpA-features 16/143 (11%) had radiographic sacroiliitis and 35/143 (24.5%) patients had a positive MRI-SI. Of the patients with normal radiographs 70/127 (55%) had neither a positive MRI-SI nor HLA-B27 and 11/127 (9%) were diagnosed with axSpA. In total, 62/143 (43%) patients were diagnosed with axSpA. All patients with radiographic sacroiliitis were diagnosed with axSpA. When the ASAS axSpA classification criteria were applied, 22 patients without a diagnosis of axSpA fulfilled the ASAS-criteria and 11 patients with an axSpA diagnosis did not fulfil the ASAS-criteria and.

In patients with 3 SpA-features 5/79 (6%) had radiographic sacroiliitis and 29/79 (38%) had a positive MRI-SI. Of the patients with normal radiographs 29/74 (39%) had neither a positive MRI-SI nor HLA-B27 and 8/74 (11%) were diagnosed with axSpA. In total, 49/79 (62%) patients were diagnosed with axSpA. All patients with radiographic sacroiliitis were diagnosed with axSpA. When the ASAS axSpA classification criteria were applied, 9 patients without a diagnosis of axSpA fulfilled ASAS-criteria and 8 patients with an axSpA diagnosis did not fulfil the ASAS-criteria.

In patients with ≥4 SpA-features 28/119 (24%) had radiographic sacroiliitis and 47/119 (40%) had a positive MRI-SI. Of the 91 patients with normal radiographs 42 (46%) had neither a positive MRI-SI nor HLA-B27 and 28/91 (31%) were diagnosed with axSpA. In total, 101/119 (85%) patients were diagnosed with axSpA. Again, all patients with radiographic sacroiliitis (28/28) were diagnosed with axSpA. Remarkably, 18/119 patients (15%) with ≥4 SpA-features but with negative imaging were not given the diagnosis axSpA, 4 of whom were HLA-B27 positive. When the ASAS axSpA classification criteria were applied, 4 patients without a diagnosis of axSpA fulfilled ASAS-criteria and 28 patients with an axSpA diagnosis did not fulfil the ASAS-criteria. Moreover, patients with ≥4 features not diagnosed with axSpA were mostly given the diagnosis non-specific back pain and degenerative disc disease (data not shown). In these patients the most common SpA-features were a positive family history for SpA (67%), good response to NSAIDs (82%), and IBP (94%).

Table 1 Baseline characteristics of patients with chronic back pain in the SPACE-cohort and stratified by total number of SpA-features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging.

Characteristic	All patients, *n*=500	Patients with ≤1 features, *n*=159
Age, years	29.3 (8.3)	29.7 (8.8)
Symptom duration, months	13.4 (7.4)	12.9 (7.3)
Male	185 (37)	51 (32)
IBP	329 (66)	43 (27)
Good response to NSAIDs [a]	208 (42)	13 (8)
Positive family history SpA [b]	206 (41)	26 (16)
Peripheral arthritis [¥]	74 (15)	2 (1)
Dactylitis [¥]	26 (5)	0 (0)
Enthesitis [¥]	108 (22)	4 (3)
Anterior uveitis [¥]	38 (8)	2 (1)
IBD [¥]	35 (7)	8 (5)
Psoriasis [¥]	57 (11)	2 (1)
Elevated CRP (mg/L) / ESR (mm) [c]	132 (26)	12 (8)
HLA-B27 positive	198 (40)	36 (23)
Imaging°		
X-SI positive **	58 (12)	9 (6)
MRI-SI positive **	146 (29)	33 (21)
Diagnosis axSpA [d]	250 (50)	38 (24)

Results are presented as mean ± SD or number (%). [¥] Past or present condition, either confirmed or diagnosed by a physician. IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; °According to global assessment radiologist (local reading). ** X-SI, radiograph of sacroiliac joints;

Patients with 2 features, *n*=143	Patients with 3 features, *n*=79	Patients with ≥ 4 features, *n*=119
28.8 (8.3)	29.1 (8.0)	29.5 (7.9)
14.6 (7.7)	13.3 (7.0)	12.7 (7.4)
56 (39)	24 (30)	54 (45)
103 (72)	71 (90)	112 (94)
50 (35)	47 (60)	98 (82)
57 (40)	43 (54)	80 (67)
15 (11)	11 (14)	46 (39)
1 (1)	3 (4)	22 (19)
12 (8)	15 (19)	77 (65)
9 (6)	6 (8)	21 (18)
7 (5)	7 (9)	13 (11)
7 (5)	8 (10)	40 (34)
25 (18)	26 (33)	69 (58)
65 (46)	41 (52)	56 (47)
16 (11)	5 (6)	28 (24)
37 (26)	29 (37)	47 (40)
62 (43)	49 (62)	101 (85)

MRI-SI, magnetic resonance imaging of sacroiliac joints. AxSpA, axial spondyloarthritis. [a] Back pain not present anymore or is much better 24–48 hours after a full dose of NSAID. [b] Presence in first- or second degree relatives of any of the following: ankylosing spondylitis, psoriasis, acute anterior uveitis, reactive arthritis, or inflammatory bowel disease. [c] Values greater than the upper limit of normal. [d] Diagnosis based on information after full diagnostic work-up: medical history, physical examination, imaging, and laboratory testing.

Table 2 Diagnosis and classification of patients (n=500) with ≤1, 2, 3 and ≥4 spondyloarthritis (SpA)-features after medical history taking, physical examination and measurement of acute phase reactants, followed by sacroiliac imaging and HLA-B27 testing.

Number of SpA-features	X-SI status	HLA-B27/MRI status
0-1 n=159	X-SI+ n=9	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- n=150	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
Mean level of confidence regarding diagnosis (SD)		
2 n=143	X-SI+ n=16	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- n=127	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
Mean level of confidence regarding diagnosis (SD)		
3 n=79	X-SI+ n=5	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- n=74	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-

Rheumatologist SpA diagnosis yes	Rheumatologist SpA diagnosis no	ASAS axSpA classification yes	ASAS axSpA classification no
4		4	
1	1	2	
1		1	
2		2	
6	1	7	
7	16		23
15	6	14	7
2	97		99
6.9 (2.3)	7.5 (2.4)		
14		14	
1		1	
1		1	
15		15	
15	20	35	
5	2	7	
11	59		70
7.6 (1.9)	6.7 (2.3)		
3		3	
1		1	
1		1	
17		17	
11	9	20	
8		8	
8	21		29

Table 2 Continued.

Number of SpA-features	X-SI status	HLA-B27/MRI status
Mean level of confidence regarding diagnosis (SD)		
≥ 4 *n*=119	X-SI+ *n*=28	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- *n*=91	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
Mean level of confidence regarding diagnosis (SD)		

X-SI, radiograph of sacroiliac joints; HLA-B27, human leucocyte antigen B27; MRI-SI, magnetic resonance imaging of sacroiliac joints; Imaging according to global assessment radiologist (local reading). Diagnosis based on information after full diagnostic work-up: medical history, physical examination, imaging, and laboratory testing.

Rheumatologist SpA diagnosis yes	Rheumatologist SpA diagnosis no	ASAS ax SpA classification yes	ASAS axSpA classification no
8.0 (1.9)	7.1 (2.0)		
15		15	
8		8	
5		5	
16		16	
21	4	25	
8		8	
28	14		42
8.0 (2.0)	7.3 (1.7)		

ASAS axSpA criteria, Assessment of SpondyloArthritis international Society criteria for axial spondyloarthritis. Mean level of confidence regarding diagnosis: 0 (not confident at all) through 10 (very confident).

Overall, the mean levels of confidence (SD) regarding a diagnosis of axSpA and no axSpA were 7.7 (2.0) and 7.2 (2.3), respectively. Mean levels of confidence of axSpA diagnosis for the different patient subgroups rose with the presence of more SpA-features; ≤1 feature, mean 6.9 (2.3); 2 features, mean 7.6 (1.9); 3 features, mean 8.0 (1.9); ≥4 features, mean 8.0 (2.0) (**Table 2**).

With the clinical diagnosis of the rheumatologist as the gold standard, sensitivity and specificity of the ASAS classification criteria for axSpA were 76% (190/250) and 84% (210/250), respectively (**Table 3**).

In univariable analysis, HLA-B27 positivity and any positive imaging were associated with an axSpA diagnosis (OR 5.6, 95% CI 3.7 to 8.3 and OR 34.3, 95% CI 17.3 to 67.7 respectively). These associations were similar across subgroups (**Table 4 and 5**). In multivariable logistic regression analysis with clinical diagnosis as the dependent variable and SpA-features from the ASAS-criteria as independent variables HLA-B27 and positive imaging were both independent determinants of diagnosis (data not shown).

Table 3 Concordance between clinical axSpA diagnosis and meeting the ASAS classification criteria for axSpA in CBP patients with the physician's diagnosis as the gold standard in the SPACE-cohort (*n*=500). Sensitivity 76% (190/250) and specificity 84% (210/250). Positive predictive value (PPV): 190/230 (83%), negative predictive value (NPV): 210/270 (78%).

	Clinical axSpA diagnosis		
ASAS classification criteria	Yes	No	Total
Yes	190	40	230
No	60	210	270
Total	250	250	500

Table 4 Concordance between clinical axSpA diagnosis and presence of HLA-B27 for all patients and stratified for total number of SpA-features.

All patients		**Clinical axSpA diagnosis**	
HLA-B27 positive	Yes	No	Total
Yes	147	51	198
No	103	199	302
Total	250	250	500
OR (95% CI)		5.6 (3.7-8.3)	
≤1 feature		**Clinical axSpA diagnosis**	
HLA-B27 positive	Yes	No	Total
Yes	18	18	36
No	20	103	123
Total	38	121	159
OR (95% CI)		5.2 (2.3-11.6)	
2 features		**Clinical axSpA diagnosis**	
HLA-B27 positive	Yes	No	Total
Yes	45	20	45
No	17	61	78
Total	62	81	143
OR (95% CI)		8.1 (3.8-17.1)	
3 features		**Clinical axSpA diagnosis**	
HLA-B27 positive	Yes	No	Total
Yes	32	9	41
No	17	21	38
Total	49	30	79
OR (95% CI)		4.4 (1.7-11.7)	
≥4 features		**Clinical axSpA diagnosis**	
HLA-B27 positive	Yes	No	Total
Yes	52	4	56
No	49	14	63
Total	101	18	119
OR (95% CI)		3.7 (1.1-12.1)	

HLA-B27, human leucocyte antigen B27; axSpA, axial spondyloarthritis; OR = odds ratio; 95% CI = 95% confidence interval.

Table 5 Concordance between clinical axSpA diagnosis and any positive imaging (MRI-SI and/or X-SI) for all patients and stratified for total number of SpA-features.

All patients		**Clinical axSpA diagnosis**	
Any positive imaging	Yes	No	Total
Yes	147	10	157
No	103	240	343
Total	250	250	500
OR (95% CI)		34.3 (17.3-67.7)	
≤1 feature		**Clinical axSpA diagnosis**	
Any positive imaging	Yes	No	Total
Yes	29	8	37
No	9	113	122
Total	38	121	159
OR (95% CI)		45.5 (16.1-128.3)	
2 features		**Clinical axSpA diagnosis**	
Any positive imaging	Yes	No	Total
Yes	36	2	38
No	26	79	105
Total	62	81	143
OR (95% CI)		54.7 (12.3-243)	
3 features		**Clinical axSpA diagnosis**	
Any positive imaging	Yes	No	Total
Yes	30	0 *	30
No	19	30	49
Total	49	30	79
OR (95% CI)		95.4 (5.5-1652.2)	
≥4 features		**Clinical axSpA diagnosis**	
Any positive imaging	Yes	No	Total
Yes	52	0 *	52
No	49	18	67
Total	101	18	119
OR (95% CI)		39.2 (2.3-668.8)	

axSpA, axial spondyloarthritis; X-SI, radiograph of sacroiliac joints; MRI-SI, magnetic resonance imaging of sacroiliac joints; OR, odds ratio; 95% CI, 95% confidence interval. * For computation of odds ratios in case of zeroes, 0.5 were added to all cells.

DISCUSSION

Prompted by concerns regarding overdiagnosis of axSpA we investigated whether in patients referred with recent onset CBP and a suspicion of axSpA, the presence of several SpA-features suffices for a diagnosis of axSpA. While, as expected, an increasing number of SpA-features was associated with an increased likelihood of axSpA diagnosis this association was not absolute. Numerous patients with multiple SpA-features did not get a diagnosis of axSpA. Among them are half of the HLA-B27 positive patients with 3 SpA-features but without imaging abnormalities. This example clearly shows that a clinical diagnosis is based on more than simply a sum of features.

In this cohort the ASAS classification criteria had an overall sensitivity and specificity of 76% and 84%, respectively. This is comparable to those found in the original ASAS-cohort. In line with the finding that patients with multiple SpA-features are not always diagnosed with axSpA 17% of patients that on paper met the ASAS classification criteria, which requires presence of at least two SpA-features, were not diagnosed with axSpA.

An important finding is the prominent -if not dominant- role of imaging and HLA-B27 testing in diagnosing axSpA in rheumatology clinics. The statistically stronger association between positive imaging and axSpA diagnosis as compared to HLA-B27 and axSpA diagnosis (or any other SpA-feature) should be interpreted with caution. The prevalence of axSpA in this cohort of patients specifically referred to the rheumatologist (50%) is much higher than the prevalence of axSpA in unselected CBP patients, and we do not know which screening tools were applied to select patients for referral. In our cohort X-SI was positive in only a minority of patients whilst an analysis of 204 referral letters indicated that HLA-B27 positivity was mentioned four times more often than a positive MRI-SI as a reason for referral (unpublished data). This difference in absolute prevalence implies that the impact of different ORs (OR=5.6 for HLA-B27 and OR=35 for imaging) may be far more similar than the ORs suggest.

Nevertheless, our findings stress the dominance of imaging in establishing an axSpA diagnosis and add to the importance of a proper interpretation of the images.[15-17]

At first sight, some of the diagnoses may raise suspicion. For instance, a diagnosis of axSpA may not be expected in HLA-B27 negative patients that have normal imaging tests, and only a few other SpA-features. In such patients, a diagnosis may still be justifiable because of features or symptoms that are not part of the ASAS-criteria, e.g. buttock pain, IBP according

to Calin or Berlin criteria, presence of structural (but not active) lesions on MRI-SI or spinal inflammatory lesions, even though the latter two manifestations are rare in the absence of bone marrow edema on MRI-SI.[18]

Furthermore, differences in the interpretation of imaging may also have contributed to unexpected diagnoses. Even though the assessment of the radiologist was used for the analyses, the rheumatologist has provided the diagnosis and may -based on the clinical symptoms- have overruled the radiologist's report, for instance by taking structural lesions or spinal inflammatory lesions into account.[18, 19]

A possible limitation of this study is that the clinical diagnosis - as is usual in clinical practice - was provided by only one rheumatologist. Each rheumatologist may consider different features, apart from positive imaging and presence of HLA-B27, being most informative for axSpA diagnosis. Even though this was not assessed it is conceivable this might have influenced the diagnosis. Future studies should definitely assess interobserver variance in clinical diagnosis.

The ASAS modified Berlin algorithm can be used by rheumatologists in the clinical decision making process when diagnosing CBP patients. But blindly applying the ASAS modified Berlin algorithm will also result in false-positive and false-negative diagnoses. As has become clear in our study, in patients without radiographic sacroiliitis but with multiple SpA-features (and/or presence of HLA-B27), the algorithm immediately leads to an axSpA diagnosis, while in clinical practice this is not always clear. In 15% of the patients with ≥4 SpA-features and 13% of the HLA-B27 positive patients with 2-3 SpA-features that should have a clinical diagnosis of axSpA according to the algorithm, such a diagnosis was not confirmed by the clinician.

While the SPACE-cohort is running in different countries and settings (academic and non-academic), we did not find an important center effect. In all centers the likelihood of axSpA diagnosis similarly increased by an increasing number of SpA-features, which adds to the credibility of our data. Nevertheless, patients were diagnosed by hospital-based rheumatologists with an expertise in diagnosing patients with axSpA, and results of this study cannot be extrapolated to different clinical settings such as primary care and common rheumatology practices or those of other medical specialities.

In conclusion, in clinical practice the mere presence of SpA-features does not automatically result in a clinical diagnosis of axSpA. Furthermore, this study confirms that the ASAS modified

Berlin algorithm could be used as a guidance tool but that a thorough diagnostic work-up with ample consideration for alternative diagnoses is still mandatory. Preferably, all information including imaging of sacroiliac joints and presence of HLA-B27 should be available to the rheumatologist to come to a final diagnosis.

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SUPPLEMENTARY MATERIAL

Table S1. Diagnosis of axSpA in participating centers for all patients and stratified for total number of SpA-features.

	All patients n=250	≤1 features, n=38
Diagnosis axSpA per center		
1. Leiden (n_{total}=298)	119 (39.9)	23/123 (18.7)
2. Padova (n_{total}=50)	50 (100)	0 (0)
3. Oslo (n_{total}=87)	53 (60.9)	9/18 (50)
4. Amsterdam (n_{total}=42)	19 (45.2)	6/14 (42.9)
5. Gouda (n_{total}=23)	9 (39.1)	0/4 (0)

Diagnosis based on information after full diagnostic work-up: medical history, physical examination, imaging, and laboratory testing. Patient data available from the following centers: Leiden University Medical Center (LUMC), Leiden, the Netherlands;

2 features, n=62	3 features, n=49	≥4 features, n=101
44/99 (44.4)	24/40 (60)	28/36 (77.7)
0 (0)	6/6 (100.0)	44/44 (100.0)
13/23 (56.5)	13/21 (61.9)	18/25 (72.0)
3/14 (21.4)	3/7 (42.9)	7/7 (100)
2/7 (28.6)	3/5 (60.0)	4/7 (57.1)

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