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ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort

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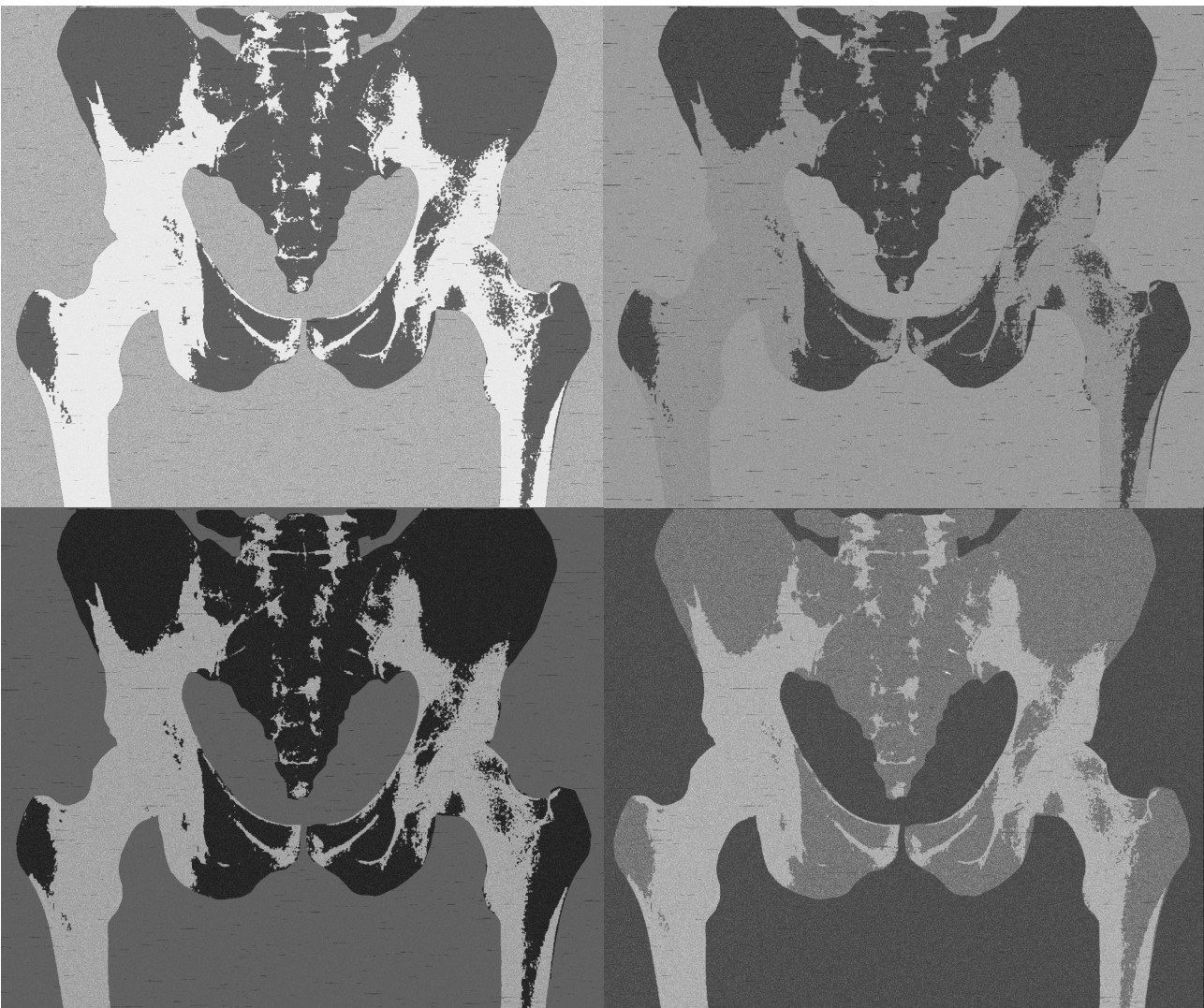

Abstract

Objective

To compare the original Berlin algorithm for diagnosing axial Spondyloarthritis (axSpA) with two modifications in the SPondyloArthritis Caught Early (SPACE)- cohort and the Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria validation (ASAS)-cohort.

Methods

Patients in the SPACE-cohort (back pain ≥3 months, ≤2 years, onset <45 years) and the ASAS-cohort (undiagnosed chronic back pain) were diagnosed according to three algorithms: original (inflammatory back pain (IBP) mandatory), modification 1 (IBP defined by ≥3/5 IBP-features instead of ≥4/5) and modification 2 (IBP deleted as obligatory entry criterion, added as SpA-feature). Diagnosis by rheumatologist, ASAS axSpA criteria and likelihood ratio product were used as external standards to test the performance of the algorithms.

Results

SPACE-cohort: Compared to the diagnosis by rheumatologist (either axSpA or no axSpA), the original algorithm agreed in 120 patients (76.4%). Agreement decreased using modification 1 (119 patients; 75.8%), increased using modification 2 (125 patients; 79.6%). Sensitivity increased from 66.2% (original) to 72.3% (modification 1) and 78.5% (modification 2). Specificity decreased more using modification 1 (83.7% to 78.3%) than when using modification 2 (83.7% to 79.6%).
ASAS-cohort: Compared to the diagnosis by rheumatologist (either axSpA or no axSpA), the original algorithm agreed in 484 patients (70.7%). Agreement increased using modification 1 (520 patients; 75.9%) and modification 2 (548 patients; 80.0%). Sensitivity increased from 65.3% (original) to 77.9% (modification 1) and 79.6% (modification 2). Specificity decreased more using modification 1 (79.2% to 72.2%) than when using modification 2 (79.2% to 75.6%).

Conclusions

ASAS accepted a modified algorithm for diagnosing axSpA in which IBP is excluded as obligatory entry criterion and added as SpA-feature.

Introduction

Spondyloarthritis (SpA) consists of a heterogeneous group of inter-related rheumatic diseases, divided into categories according to the predominant site of involvement: axial SpA (axSpA) or peripheral SpA. AxSpA is the overall umbrella term for both patients with damage visible on radiographs of the sacroiliac joints (X-SI) and nonradiographic axSpA. The heterogeneity of SpA makes early detection challenging [1]. A helpful tool in the early diagnosis of axSpA is the Berlin diagnostic algorithm; a decision tree applicable to patients with inflammatory back pain (IBP).

The algorithm is fully based on data from the literature on the sensitivity and specificity of characteristic SpA-features. The likelihood ratio (LR)-product of (past or current) SpA-features is calculated for each patient as they follow the algorithm taking into account the a priori probability of SpA, thereby avoiding unnecessary diagnostic tests. The algorithm consists of several diagnostic steps, of which assessment of IBP is the first critical step. Patients may follow the algorithm in various ways depending on whether they have sacroiliitis on x-ray, the number of (past or current) SpA-features, human leukocyte antigen (HLA)-B27 positivity and sacroiliitis on MRI.

Since only 70–80% of patients with axial SpA have typical IBP symptoms, IBP as an obligatory entry criterion in the algorithm has some limitations because patients with axSpA but without IBP will not be captured [2–5]. To circumvent this limitation, it was proposed in 2004 that in back pain patients without IBP other causes of back pain should be considered in general, unless SpA is suspected because of the presence of other SpA-features. This recommendation, however, was not further specified in the original algorithm.

This has stimulated us to test two modifications of the algorithm in two independent cohorts; an observational inception cohort including patients with chronic back pain (the SPondyloArthritis Caught Early (SPACE)-cohort) and a larger, international cohort created for the validation of the new Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria (the ASAS-cohort).

Methods

SPACE-cohort

Patients with chronic (almost daily) back pain for ≥3 months but ≤2 years, with the onset <45 years University Medical Center, were included in the SPACE-cohort since January 2009. At baseline, patients underwent a diagnostic work-up consisting of physical examination, MRI and X-rays of the SI-joints (MRI-SI and X-SI) and laboratory assessments including HLA-B27 testing (online supplementary text 1). Furthermore, the presence of SpA-features is recorded (online supplementary table S1) [2]. After that, a rheumatologist experienced in SpA diagnosed all patients as having SpA or no SpA.

All MRI-SIs and X-SIs were independently scored by two trained readers (MdH and RvdB) according to the ASAS/ OMERACT definition (MRI-SI) [6], and the modified New York (mNY) criteria (X-SI) [7]. A third trained reader (VNC) served as adjudicator and scored only the images in which the first two readers disagreed. If two/three readers scored positive, the image was scored accordingly. All readers were blinded for clinical and laboratory data, and for the results of the other imaging method.

ASAS-cohort

The ASAS-cohort was compiled for the validation of the new classification criteria for axSpA. Patients with chronic back pain of ≥3 months with onset <45 years and with a suspicion of SpA but without a definite diagnosis were included and assessed according to a fixed protocol by rheumatologists who are experts in the field of SpA.

Complete and detailed data collection of the ASAS-cohort has been described before [8]. This included assessment of (past or current) SpA-features [2], C-reactive protein, and HLA-B27 typing. Plain radiographs of the pelvis were taken in all patients. The local rheumatologist and/or radiologist assessed sacroiliitis on X-SI (mNY criteria) [9], and the presence or absence of typical signs of active inflammation on MRI-SI [8].

Diagnosis of patients according to the Berlin algorithm

According to the original algorithm (figures 1A and 2A), patients were diagnosed as having axSpA if they had IBP and ≥3 SpA-features, or if patients had IBP with 1-2 SpA-features and were HLA-B27 positive. Patients with no other SpA-features besides IBP could only be diagnosed as having axSpA if both HLA-B27 and active sacroiliitis (MRI-SI) were present.
In the original algorithm, IBP was defined according to the Calin criteria [10]. In the SPACE-cohort and ASAS-cohort, however, IBP was defined according to the 'ASAS expert criteria', which are slightly more specific [5].
Subsequently, two modifications of the algorithm were constructed. In modification 1, fulfilllment of the ASAS IBP criteria [11], was adapted (figures 1B and 2B). The IBP criteria are: onset of back pain before the age of 40, insidious onset, improvement of back pain with exercise, no improvement of back pain with rest and pain at night with improvement upon getting up [5]. Patients who fulfilled ≥3 IBP criteria instead of ≥4 out of 5 criteria could now be diagnosed as having IBP. During validation of these ASAS IBP criteria sensitivity (79.6%) and specificity (72.4%) were found to be best when patients fulfilled ≥4/5 criteria, a higher sensitivity (95.1%) was reached at the cost of specificity (47.5%) if ≥3/5 criteria for IBP were considered sufficient [5, 12].
Modification 2 slightly changed the structure and the set of SpA-features by deleting IBP as obligatory entry criterion, and adding it as SpA-feature. This resulted in three entry groups based on the requirement of ≥4, 2-3 and 0-1 SpA-features (figures 1C and 2C). All patients were diagnosed according to the three algorithms.

Statistical methods

The disease probability in each patient was calculated by multiplying the individual likelihood ratios (LRs) of all identified SpA-features. An LR-product of 79 results in a positive predictive value of 80% in patients with chronic back pain with an assumed disease prevalence of axSpA of 5% [2]. Missing values for the presence of SpA-features were interpreted as being absent and were included in the following analyses with the missing values set as 'negative'. Because of the lack of a true gold standard, the fulfilllment of the ASAS axSpA criteria [7], the disease probability based on the likelihood ratio (LR)-product [13], and the diagnosis by the rheumatologist were used as external standards to test the performance of the algorithms. The performance was assessed by calculating the sensitivity, specificity, percentage of agreement on the diagnosis as well as the percentage of patients erroneously diagnosed as axSpA and/or diagnosis of axSpA missed by the algorithm.

Results

Baseline characteristics

SPACE-cohort

In total, 157 patients were included in the analyses of the SPACE-cohort. The rheumatologist diagnosed axSpA in 65/157 (41.4%) of the patients. Characteristics are presented in table 1.

Table 1: Baseline characteristics of patients in the SPACE-cohort and the ASAS-cohort; SpA versus no SpA based on the diagnosis of the rheumatologist.

	SPACE-cohort*			ASAS-cohort*		
	axSpA (n=65)	**no SpA (n=92)**	**P-value**	**axSpA (n=421)**	**no SpA (n=264)**	**P-value**
Age (years) at inclusion, mean ± SD	31.5 ± 16.6	31.1 ± 8.8	0.86	31.0 ± 10.8	35.8 ± 10.5	0.839
Male, n (%)	29 (44.6)	23 (25.0)	0.01	225 (53.4)	87 (33.0)	<0.001
Duration of back pain, mean ± SD	13.4 ± 7.4 (months)	13.7 ± 7.1 (months)	0.79	6.3 ± 7.8 (years)	9.3 ± 10.7 (years)	0.792
HLA-B27 positive, n (%)	44 (67.7)	9 (9.8)	<0.001	270 (64.1)	73 (27.7)	<0.001
Pos. fam. history SpA, n (%)	31 (47.7)	25 (27.2)	0.01	106 (25.2)	52 (19.7)	0.097
IBP, n (%)	52 (80.0)	53 (57.6)	0.003	324 (77.0)	125 (47.3)	<0.001
Psoriasis, n (%)	10 (15.4)	6 (6.5)	0.07	36 (8.6)	13 (4.9)	0.073
Dactylitis, n (%)	4 (6.2)	2 (2.2)	0.20	28 (6.7)	5 (1.9)	0.005
Enthesitis, n (%)	10 (15.4)	15 (16.3)	0.88	86 (20.4)	38 (14.4)	0.046
Uveitis, n (%)	10 (15.4)	5 (5.4)	0.04	43 (10.2)	21 (8.0)	0.323
IBD, n(%)	4 (6.2)	5 (5.4)	0.85	14 (3.3)	4 (1.5)	0.149
Preceding infection, n (%)	2 (3.1)	0 (0.0)	0.09	12 (0.17)	5 (0.14)	0.434
CRP (mg/l), mean ± SD	8.3 ± 11.6	5.7 ± 6.9	0.11	7.1 ± 14.9	2.4 ± 4.4	<0.001
ESR (mm/h), mean ± SD	13.6 ± 16.3	10.4 ± 10.7	0.17	#	#	
Alternating buttock pain, n (%)	15 (23.1)	18 (19.6)	0.60	174 (41.3)	65 (24.6)	<0.001
Good response to NSAIDs, n (%)	27 (41.5)	27 (29.3)	0.11	259 (61.5)	73 (27.7)	<0.001
Elevated CRP/ESR, n (%)	15 (23.1)	16 (17.4)	0.38	170 (40.4)	43 (16.3)	<0.001
Arthritis, n (%)	13 (20.0)	10 (10.9)	0.11	171(40.6)	59 (22.3)	<0.001
Sacroiliitis X-ray, n (%)	11 (16.9)	1 (1.1)	<0.001	123 (29.2)	9 (3.4)	<0.001
Sacroiliitis MRI, n (%)	27 (41.5)	0 (0.0)	<0.001	202 (48)	8 (3)	<0.001

* Diagnosis according to rheumatologist. # Not estimated in ASAS-cohort. P-values <0.05 are defined statistically significant. HLA-B27, Human Leukocyte Antigen; IBP, Inflammatory Back Pain; preceding infection can be balinitis, urethritis, cervicitis and/or acute diarrhea; CRP, C-reactive protein; IBD, Inflammatory Bowel Disease; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

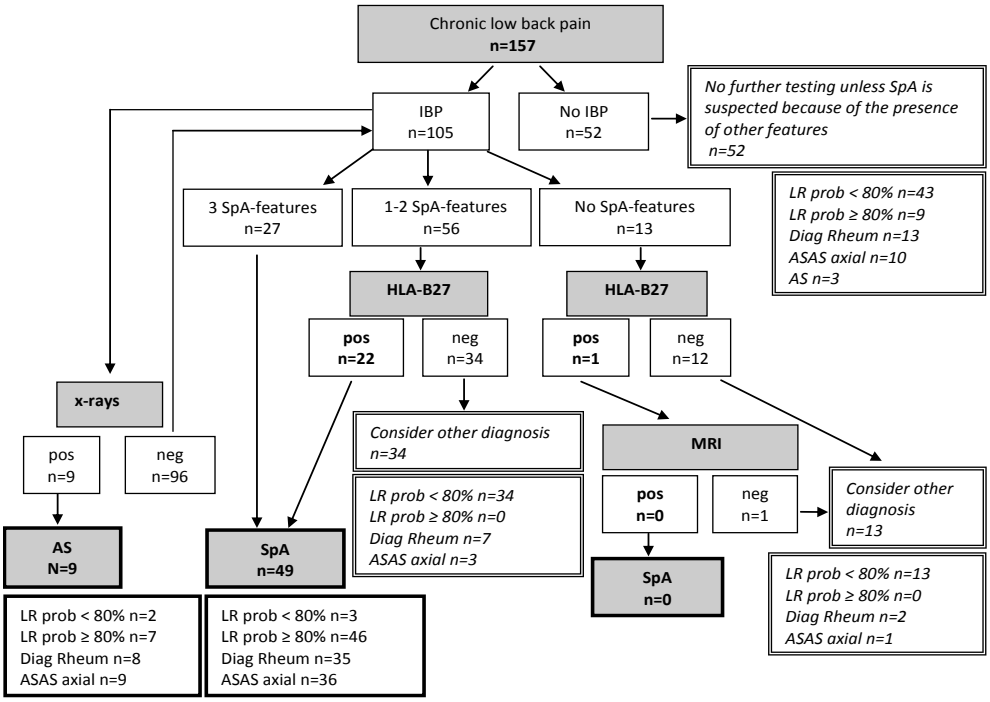

Figure 1a: Original Berlin algorithm (SPACE-cohort).

ASAS-cohort

From the 685 patients of the ASAS-cohort used in this study, 421 (61.5%) were diagnosed as axSpA by the rheumatologist. Characteristics are presented in table 1.

Diagnosis by the algorithms

SPACE-cohort

According to the original algorithm, 58 patients were diagnosed as having axSpA. Nine of them were diagnosed as ankylosing spondylitis (AS), based on the presence of radiographic sacroiliitis, 27 patients had axSpA based on clinical grounds (≥3 SpA-features present), the remaining 22 patients were HLA-B27 positive with 1-2 SpA-features present (figure 1A).
According to modification 1, 22 patients immediately leave the algorithm. A total of 56 patients are diagnosed as having axSpA: 11 patients are directly diagnosed as AS, 29 patients had ≥3 SpA-features and 27 HLA-B27 positive patients had 1-2 SpA-features (figure 1B).
In modification 2, 69 patients were diagnosed as having axSpA: 12 patients were diagnosed as AS, 27 patients had ≥4 SpA-features and 29 patients were HLA-B27 positive and had 2-3 SpA-features. In addition, there was one patient with 0-1 SpA-features, HLA-B27 positivity and a positive MRI-SI who was diagnosed as having SpA (figure 1C).

Table 2: Sensitivity, specificity, percentage of axSpA diagnosis missed and erroneously diagnoses of axSpA by the algorithm in the SPACE-cohort and ASAS-cohort according to the three external standards ASAS axial SpA criteria, LR-product probability ≥ 80% and diagnosis rheumatologist.

	Sensitivity (%)	Specificity (%)	Correct classified (%)	False-negatives (%)	False-positives (%)
SPACE					
ASAS axial SpA					
Original	72.6	86.3	80.9	10.8	8.3
Modification 1	81.7	81.4	81.5	7.0	11.5
Modification 2	89.8	83.7	86.0	3.8	10.2
LR-product probability ≥80%					
Original	85.5	94.7	91.1	5.7	3.2
Modification 1	92.4	93.4	93.0	3.2	3.8
Modification 2	100	92.6	95.5	0.0	4.5
Diagnosis rheumatologist					
Original	66.2	83.7	76.4	14.0	9.6
Modification 1	72.3	78.3	75.8	11.5	12.7
Modification 2	78.5	80.4	79.6	8.9	11.5
ASAS					
ASAS axial SpA					
Original	72.6	84.1	77.5	15.6	6.9
Modification 1	86.7	78.3	83.1	7.6	9.3
Modification 2	89.4	83.0	88.8	6.1	7.6
LR-product probability ≥80%					
Original	83.5	99.3	90.2	9.5	0.3
Modification 1	96.0	85.6	91.2	2.2	6.6
Modification 2	97.2	90.7	96.6	1.6	4.2
Diagnosis rheumatologist					
Original	65.3	79.2	70.7	21.3	8.0
Modification 1	77.9	72.2	75.9	13.6	10.8
Modification 2	79.6	75.6	80.0	12.7	9.8

Modification 1: IBP 3/5 instead of 4/5. Modification 2: IBP as additional SpA-feature instead of entry criterion. LR-product: Likelihood Ratio-product.

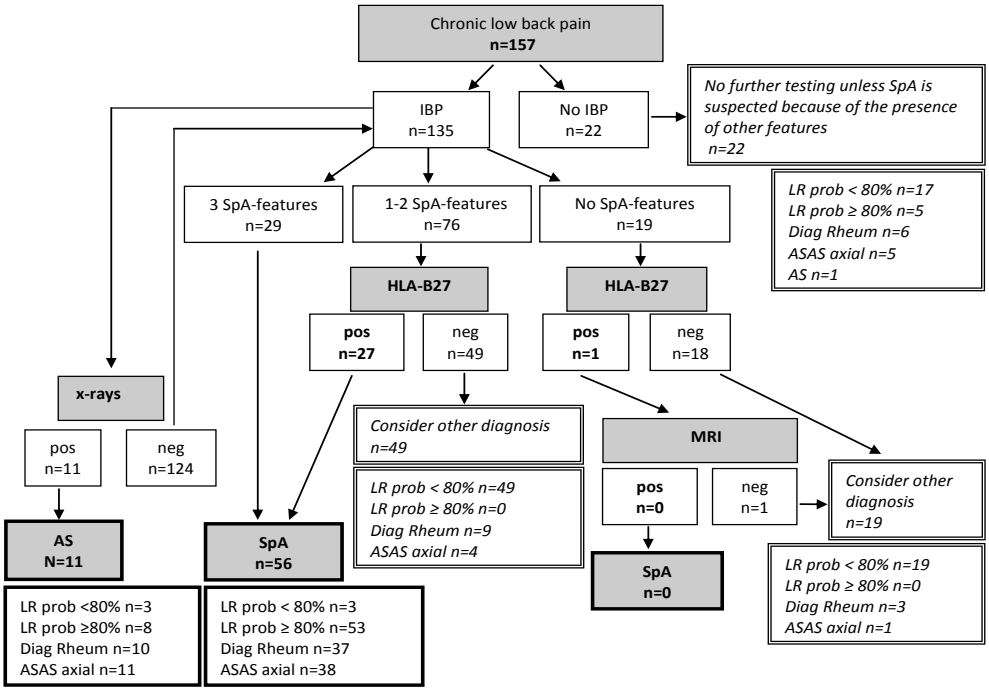

Figure 1b: Modification 1 of the Berlin algorithm; IBP defined when 3 out of 5 criteria are fulfilled instead of 4 out of 5 criteria (SPACE-cohort).

In 120 patients (76.4%) the diagnosis of the rheumatologist and the original algorithm agreed. Modification 1 (IBP 3/5) diagnosed nine more patients as having axSpA, and modification 2 (IBP excluded as obligatory entry criterion) diagnosed 11 more patients as having axSpA, resulting in agreement with the diagnosis of the rheumatologist in 119 (75.8%) and 125 patients (79.6%) respectively (table 2). Compared to the diagnosis of the rheumatologist as external standard, sensitivity was 66.2% using the original algorithm. Sensitivity was higher, 77.9% (+11.7% compared to the original algorithm) using modification 1 and increased more using modification 2, 79.6% (+13.4%). Yet specificity slightly decreased from 83.7% using the original algorithm to 78.3% (−5.4%) using modification 1 and to 80.4% (−3.3%) using modification 2. The same trend was observed compared to the other external standards. The best balance between sensitivity and specificity is present in modification 2 (table 2).

ASAS-cohort

In the original algorithm (figure 2A), 236 patients immediately leave the algorithm. Out of the 449 patients that continue in the algorithm, 330 were diagnosed as having axSpA: 102 fulfilled the mNY criteria for AS, 138 patients with ≥3 SpA-features and another 86 HLA-B27 positive patients with 1-2 SpA-features are diagnosed as having axSpA. In addition, four HLA-B27 positive patients with active sacroiliitis (MRI-SI), but without other SpA-features are diagnosed as having axSpA. In all HLA-B27 negative patients with 1-2 SpA-features (n=93), patients without SpA-features (n=19) and patients without sacroiliitis (MRI-SI) (n=7), the algorithm suggests another diagnosis than axSpA.

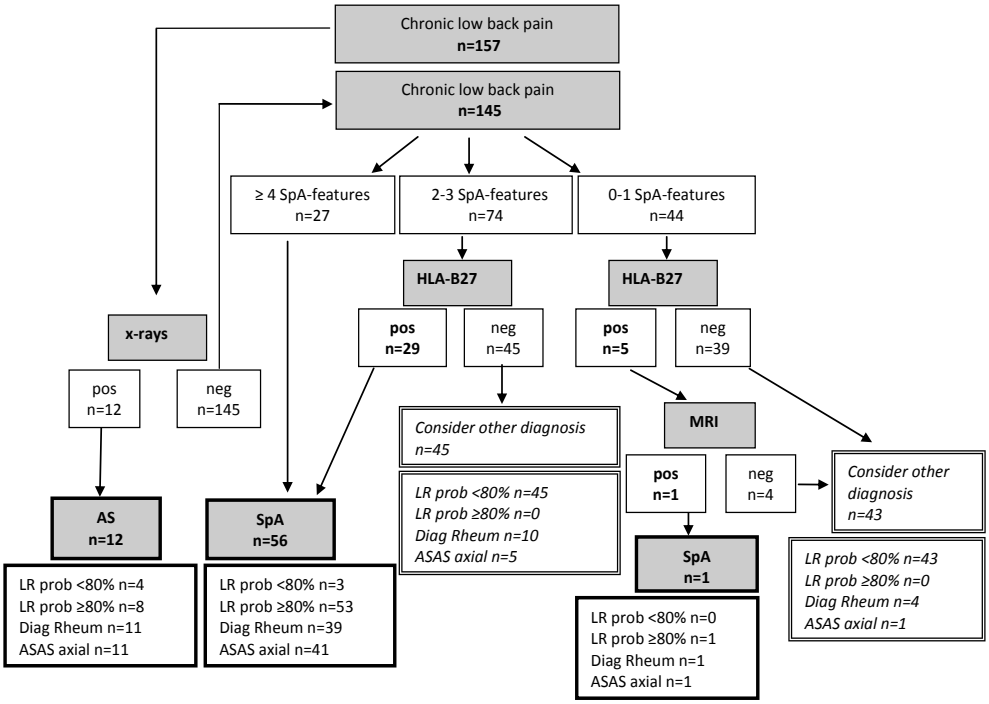

Figure 1c: Modification 2 of the Berlin algorithm; IBP is deleted as entry criterion and implemented as an additional SpA-feature (SPACE-cohort).

In modification 1 (figure 2B), 113 patients immediately leave the algorithm and 402 patients are diagnosed as having axSpA: 122 patients are directly diagnosed as AS, 164 patients with ≥3 SpA-features, 111 HLA-B27 positive patients with 1-2 SpA-features and five HLA-B27 positive patients with a positive MRI-SI but without SpA-features. In 150 HLA-B27 negative patients and in 10 HLA-B27 positive patients with a negative MRI-SI, the algorithm suggested another diagnosis than axSpA.
In modification 2 (figure 2C), the number of patients immediately leaving the algorithm is reduced to 17 patients. In total, 407 patients are diagnosed as having axSpA. Of those, 132 patients are directly diagnosed as AS, 148 patients with ≥4 SpA-features are diagnosed as having axSpA, as were 115 HLA-B27 positive patients with 2-3 SpA-features and 12 HLA-B27 positive patients with a positive MRI-SI and 0-1 SpA-features. For the remaining 278 patients another diagnosis than axSpA should be considered.
The rheumatologist diagnosis and the original algorithm agreed in 70.7% of the patients. Modification 1 showed agreement with the diagnosis of the rheumatologist in 75.9% of the patients (+5.2% compared to the original algorithm). Modification 2 showed a similar trend; 80% (+9.3% compared to the original algorithm) agreement. Sensitivity increased from 65.3% in the original algorithm to 77.9% (+12.6%) in modification 1 and 79.6% (+14.3%) in modification 2, when using the diagnosis of the rheumatologist as external standard. Specificity decreased from 79.2% in the original algorithm to 72.2% (−7.0%) in modification 1 and to 75.6% (−3.6%) in modification 2 (table 2). The performance of the three algorithms with the ASAS axSpA criteria and the LR-product as external standard are also presented in table 2 and show similar results.

Asymmetrical arthritis

In additional calculations on the performance, we replaced the SpA-feature 'peripheral arthritis' with 'asymmetrical arthritis preferentially of the lower limbs' (only performed in the ASAS-cohort). When doing so, sensitivity decreased while specificity increased in all three algorithms (online supplementary text 2).

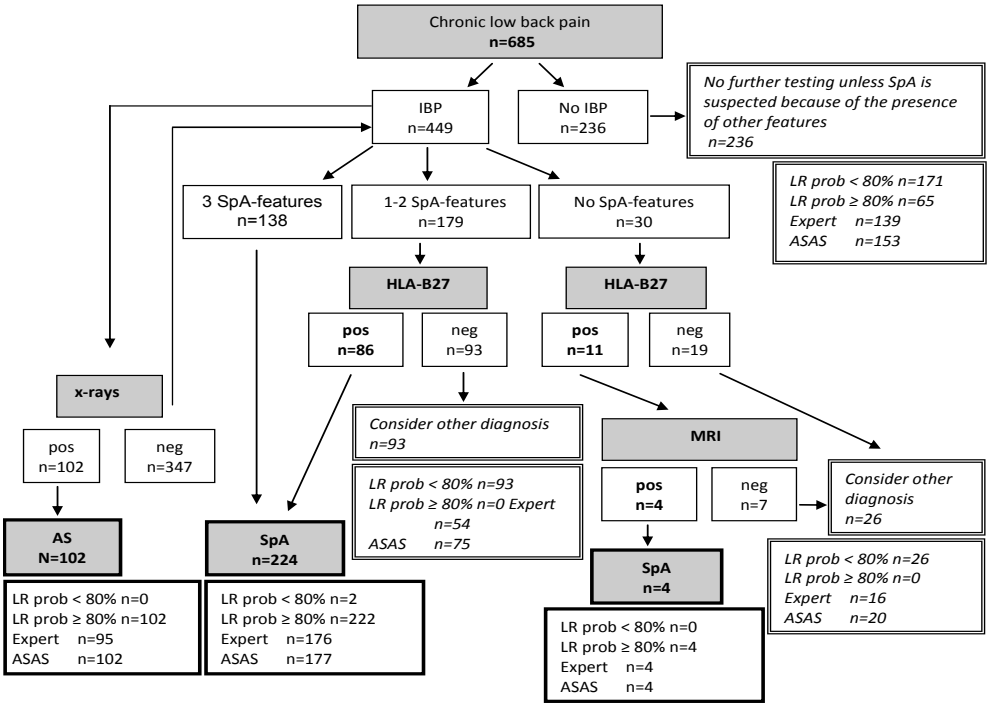

Figure 2a: Original Berlin algorithm (ASAS-cohort).

Reasons for misdiagnoses

SPACE-cohort

Compared to the diagnosis of the rheumatologist as external standard, 15 patients (9.6%) were erroneously diagnosed as having axSpA by the original algorithm and in 22 patients (14.0%) the diagnosis axSpA was missed by the algorithm, especially in the group of patients without IBP. In both modifications, a few more patients, n=20 by modification 1 and n=18 by modification 2, were erroneously diagnosed as having axSpA (12.7% (+3.2% compared to the original algorithm) by modification 1 and 11.5% (+1.9%) by modification 2) but the number of patients in which the diagnosis axSpA was missed dropped to 18 (11.5% by modification 1 (−3.8% compared to the original algorithm)) and 14 patients (8.9% by modification 2 (−7%)) (table 2).

Table 3: Misdiagnoses by the three versions of the Berlin algorithm in the SPACE-cohort (diagnosis of rheumatologist is used as external standard).

Sacroiliitis (MRI and/or X-ray)	HLA-B27 pos. or neg.	No. SpA-features	Missed diagnoses axSpA (%)	Erroneous diagnoses axSpA (%)
Original algorithm*			**n=22**	**n=15**
Imaging+	HLA-B27+	≥3	-	-
		1-2	3	-
		0	2	-
	HLA-B27-	≥3	1	1
		1-2	5	-
		0	3	-
Imaging-	HLA-B27+	≥3	1	-
		1-2	1	3
		0	1	-
	HLA-B27-	≥3	-	11
		1-2	5	-
		0	-	-
Modification 1 (IBP 3/5 instead of 4/5)*			**n=18**	**n=20**
Imaging+	HLA-B27+	≥3	-	-
		1-2	2	-
		0	-	-
	HLA-B27-	≥3	1	1
		1-2	5	-
		0	3	-
Imaging-	HLA-B27+	≥3	1	-
		1-2	-	6
		0	1	-
	HLA-B27-	≥3	-	13
		1-2	5	-
		0	-	-
Modification 2 (IBP excluded as entry criterion)		**No. SpA-features, including IBP**	**n=14**	**n=18**
Imaging+	HLA-B27+	≥4	-	-
		2-3	-	-
		0-1	-	-
	HLA-B27-	≥4	-	1
		2-3	6	-
		0-1	2	-
Imaging-	HLA-B27+	≥4	-	-
		2-3	-	6
		0-1	1	-
	HLA-B27-	≥4	-	11
		2-3	4	-
		0-1	1	-

*Patients following the original cohort and modification 1 have IBP in addition to the other SpA-features, otherwise they did not enter the algorithm, except the patients that are excluded because they had no IBP. Imaging +: sacroiliitis present on MRI and/or X-rays. Imaging -: no sacroiliitis present on MRI and/or X-rays. HLA-B27: Human Leukocyte Antigen. A list of SpA-features is given in table S1 (online supplementary material).

Table 4: Misdiagnoses by the three versions of the Berlin algorithm in the ASAS-cohort (expert opinion is used as external standard).

Sacroiliitis (MRI and/or X-ray)	HLA-B27 positive or negative	No. SpA-features	Missed diagnoses of axSpA (%)	Erroneous diagnoses of axSpA (%)
Original algorithm*			**N=146**	**n=55**
Imaging+	HLA-B27+	≥3	12	1
		1-2	17	-
		0	2	-
	HLA-B27-	≥3	7	-
		1-2	25	1
		0	8	-
Imaging-	HLA-B27+	≥3	10	-
		1-2	13	24
		0	3	-
	HLA-B27-	≥3	9	16
		1-2	37	2
		0	3	-
Modification 1 (IBP 3/5 instead of 4/5)*			**N=93**	**n=74**
Imaging+	HLA-B27+	≥3	4	2
		1-2	4	1
		0	1	-
	HLA-B27-	≥3	-	-
		1-2	24	1
		0	8	-
Imaging-	HLA-B27+	≥3	2	13
		1-2	4	34
		0	3	-
	HLA-B27-	≥3	3	21
		1-2	37	2
		0	3	-
Modification 2 (IBP excluded as entry criterion)		**No. SpA-features, including IBP**	**N=87**	**n=67**
Imaging+	HLA-B27+	≥4	-	2
		2-3	-	1
		0-1	-	-
	HLA-B27-	≥4	-	-
		2-3	25	1
		0-1	11	-
Imaging-	HLA-B27+	≥4	1	11
		2-3	1	32
		0-1	5	-
	HLA-B27-	≥4	1	17
		2-3	33	2
		0-1	10	1

*Patients following the original cohort and modification 1 have IBP in addition to the other SpA-features, otherwise they did not enter the algorithm, except the patients that are excluded because they had no IBP. Imaging +: sacroiliitis present on MRI and/or X-rays. Imaging -: no sacroiliitis present on MRI and/or X-rays. HLA-B27: Human Leukocyte Antigen. A list of SpA-features is given in table S1 (online supplementary material).

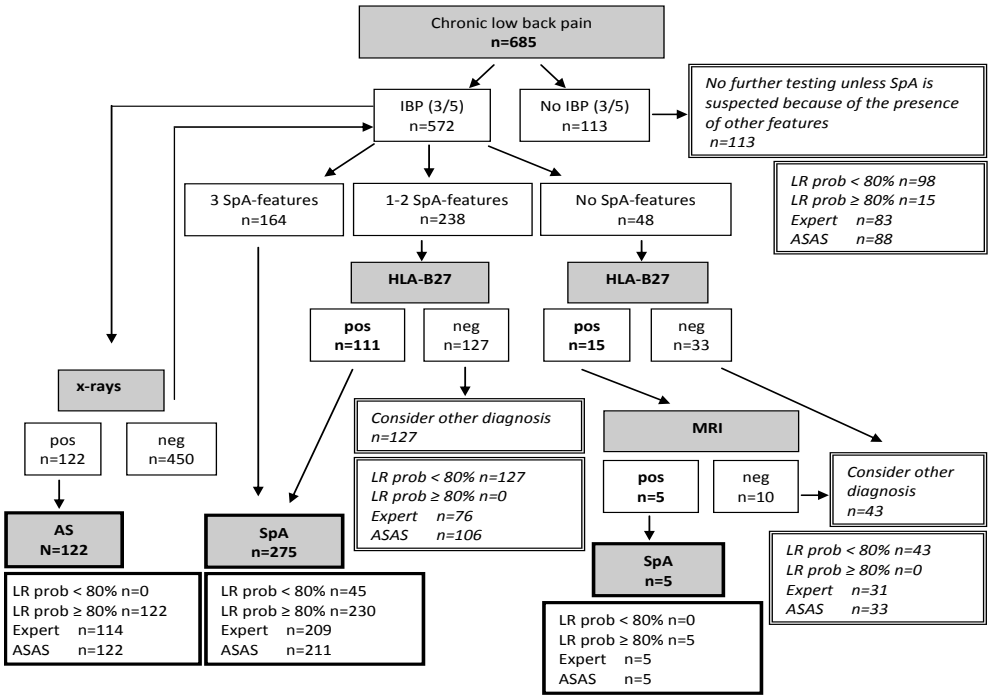

Figure 2b: Modification 1 of the Berlin algorithm; IBP defined when 3 out of 5 criteria are fulfilled instead of 4 out of 5 criteria (ASAS-cohort).

An extensive description of all misdiagnoses is given in table 3. Most patients who were erroneously diagnosed with axSpA by the algorithm have ≥4 SpA-features (including IBP) and were therefore diagnosed as SpA according to the algorithm, but are HLA-B27 negative and do not have sacroiliitis (X-SI or MRI-SI) and are not considered as having axSpA according to the rheumatologist. This pattern was seen in all three algorithms. Most patients in whom the diagnosis axSpA was missed by the algorithm are HLA-B27 negative, and have ≤3 SpA-features (including IBP) and were therefore diagnosed as no axSpA according to the algorithm. However, those patients do have sacroiliitis (MRI-SI), which is missed by the algorithm since the patients were excluded before the MRI-step. Again, this pattern was seen in all three algorithms.

ASAS-cohort

Table 2 also shows the misdiagnoses of the algorithms in the ASAS-cohort.
Using the rheumatologist diagnosis as external standard, 8.0% of the patients were erroneously diagnosed as axSpA and in 21.3% of the patients the diagnosis axSpA was missed by the original algorithm. Modification 1 showed in 10.8% (+2.8% compared to the original algorithm) of the patients an erroneous diagnosis of axSpA and in 13.6% (−7.7%) of the patients the diagnosis of axSpA was missed. Modification 2 showed a similar trend; 9.8% (+1.8%) of the patients were erroneously diagnosed as axSpA and in 12.7% (−8.6%) of the patients the diagnosis axSpAwas missed by the algorithm.
As shown in table 4, the majority of the patients (n=53) erroneously diagnosed as axSpA, have a negative MRI-SI. Two third of these patients (n=35) are HLA-B27 positive with one or more SpA-features present. This trend is seen in all three algorithms.

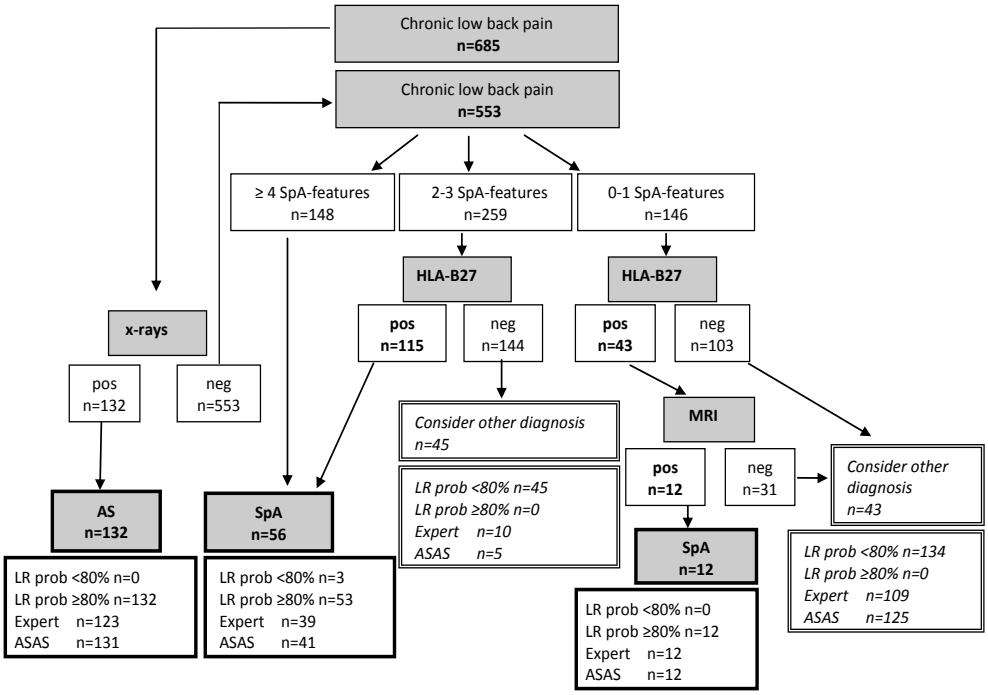

Figure 2c: Modification 2 of the Berlin algorithm; IBP is deleted as entry criterion and implemented as an additional SpA-feature (ASAS-cohort).

Most of the patients in whom the diagnosis of axSpA was missed by the algorithm are HLA-B27 negative (n=89). Almost half of these misdiagnosed patients (n=40) have a positive MRI-SI. Again, this trend is also seen using the two modifications.

Discussion

In this study we investigated the performance of the original Berlin algorithm and two modifications in the SPACE-cohort and the ASAS-cohort.

In modification 1, the ASAS criteria for IBP were defined less stringent (≥3/5 instead of ≥4/5 IBP criteria). In both cohorts this resulted in a major increase in sensitivity, while specificity only slightly decreased. Modification 2 (IBP excluded as obligatory entry criterion) resulted in an even further decrease of missed axSpA diagnoses by the algorithm. Modification 2 showed the best combination of sensitivity and specificity in both cohorts.

Our findings show that IBP as obligatory entry criterion induces too many misdiagnoses, thereby confirming the results found before of a percentage of axSpA-patients without IBP up to 30%[4, 5]. Moreover, this is also the reason that the ASAS axSpA criteria are formed without IBP as entry criterion[4, 12]. However, IBP is suitable for screening for axSpA in primary care as several studies have shown[14–16], hence also a good (albeit non-mandatory) SpA-feature, as modification 2 suggests. Also for general practitioners it is important to realise that absence of IBP does not exclude axSpA. Furthermore, a relatively young age at onset of chronic back pain is a strong signal that the back pain might be a symptom of SpA. This is one of the factors explaining the difference of the 5% of SpA in the general population at the general practitioner level, and the 61% in this age-selected population seen by rheumatologists with a special interest in SpA. It should be noted that the algorithm is intended for use by the

rheumatologist, in this specific age-defined patient population, and not in an unselected population of patients with chronic back pain.
According to all versions of the algorithm, MRI-SI is not performed in HLA-B27 negative patients with 2-3 other SpA-features; those patients leave the algorithm as no axSpA patients. In order to further decrease these missed axSpA diagnoses, it could be considered to perform MRI-SI in HLA-B27 negative (especially male) patients with 2-3 other SpA-features [17]. There are suggestions that an MRI-SI should be classified as positive on the basis of inflammatory lesions and structural changes to increase sensitivity of the MRI-SI. Moreover, there are data showing that spinal changes on MRI-spine might be present in absence of inflammation on MRI of the SI-joints, yet this accounts for no more than 5% of patients [12]. The importance of these findings in the process of diagnosis is unclear at the moment.
It was not possible to decrease the number of patients who were erroneously diagnosed as axSpA by the proposed modifications. This might be caused by the fact that this mostly concerns patients with an (atypical) presentation of ≥3 SpA-features, but who are HLA-B27 negative and do not have sacroiliitis (X-SI and/or MRI-SI). Those patients are considered by rheumatologists as no axSpA, suggesting that rheumatologists base their diagnosis, besides the total presentation, to a large extent on MRI-SI and HLA-B27 findings. For the same reasons, those patients could never be classified according to the imaging arm, nor the clinical arm of the ASAS axSpA criteria. However, missed axSpA diagnoses in 3.8% to 6.1% and erroneously diagnosed axSpA patients in 7.6% to 10.2% of the cases (table 2), is surprisingly good. This also favours using the ASAS axSpA classification criteria in a diagnostic approach.
The use of both cohorts has strengths and limitations. A limitation of the use of the ASAS-cohort is that the ASAS axSpA criteria have been validated in this cohort while the ASAS axSpA criteria are used as one of the three external standards to test the performance of the algorithms. However, this is obviated since similar results are found in the SPACE-cohort, which is independent of the validation of the ASAS axSpA criteria. A downside of the SPACE-cohort is that the diagnosis of patients was based on the judgment of a single rheumatologist, what in turn is a strong point of the ASAS-cohort where the diagnosis was made by several ASAS-rheumatologists. For both cohorts the lack of follow-up data, which reduces the certainty on the diagnosis, is a limitation.
The results of both cohorts on the performance of the three diagnostic algorithms were presented to the ASAS-members during the January 2012 meeting in Amsterdam. The membership voted for modification 2 as the diagnostic algorithm of their choice.
In conclusion, ASAS accepted a modified algorithm in which IBP is excluded as obligatory entry criterion and is added as additional SpA-feature. We have added an online figure without the data on the cohorts that can be used in daily practice (online supplementary figure S1). This modification yields a higher agreement on the diagnoses in accordance with the diagnosis by the rheumatologist, the ASAS axSpA criteria and the LR-product probability ≥80%, mainly as a result of the reduction of missed axSpA diagnoses by the algorithm. This modified algorithm might be a useful tool for rheumatologists in daily practice.

Supplementary data

Additional data are published online only. To view these files please visit the journal online (http://dx.doi.org/ 10.1136/annrheumdis-2012- 201884)

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