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Evaluation of multiple referral strategies for axial spondyloarthritis in the SPondyloArthritis Caught Early (SPACE) cohort

Ozair Abawi, Rosaline van den Berg, Désirée van der Heijde, Floris A van Gaalen

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Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to
Dr Floris A van Gaalen;
f.a.van_gaalen@lumc.nl

ABSTRACT

Background: Several models have been proposed to refer patients with possible axial spondyloarthritis (axSpA) to a rheumatologist. Our aim was to evaluate performance of these models in a single cohort.

Methods: 13 referral models found in the literature were evaluated in the Leiden SPondyloArthritis Caught Early (SPACE) cohort, which includes patients with back pain (≥3 months, ≤2 years, onset <45 years; n=261) referred to a rheumatology outpatient clinic. Imaging was not considered as a referral parameter. Performance of the strategies was evaluated (sensitivity, specificity, positive likelihood ratio (LR+)) using diagnosis by a rheumatologist as an external standard. For secondary analyses, fulfilment of the Assessment in SpondyloArthritis international Society (ASAS) axSpA criteria was used as an external standard.

Results: In total, 107/261 patients were diagnosed with axSpA. Most models performed well regarding sensitivity and specificity. The MASTER strategy showed a balanced sensitivity/specificity with the highest LR+. The ASAS and Brandt I strategies are the most sensitive strategies. Using classification by ASAS axSpA criteria as the external standard gave comparable results. Most patients missed by the strategies fulfilled the imaging arm of the ASAS axSpA criteria.

Conclusions: Most referral models performed well, although patients in SPACE have already been referred, which may have led to overestimation of performance. If no patient is to be missed, the ASAS strategy would be most preferable. If the number of referrals needs to be limited, the MASTER strategy seems to perform best. The 'ideal' referral strategy may be different from country to country, due to differences in healthcare structure and prevalence of referral parameters such as human leucocyte antigen-B27.

Key messages

What is already known about this subject?

Many strategies for referral of patients with possible axial spondyloarthritis have been published, but none have been compared head to head in a single cohort.

What does this study add?

The potential of referral strategies was clearly shown, although no referral strategy combined a high sensitivity with a high specificity. Moreover, since patients in the SPondyloArthritis Caught Early (SPACE) cohort are already referred, this may have led to an overestimation of the models.

How might this impact on clinical practice?

The study may help clinicians decide which referral strategy is most appropriate.

INTRODUCTION

Axial spondyloarthritis (axSpA), a rheumatic disease causing chronic back pain (CBP), is usually diagnosed by a rheumatologist in secondary care. However, a substantial delay between onset of symptoms and subsequent diagnosis by a rheumatologist has been reported, which is partly explained by the fact that referral of patients with possible axSpA to a rheumatologist is often delayed.[1–3] Early diagnosis of axSpA can avoid superfluous diagnostic and therapeutic interventions and can provide patients knowledge about the nature of their symptoms.[4] Moreover, effective treatment with, for instance, tumour necrosis factor (TNF) antagonists has become available in recent years, and recent therapeutic studies suggest that patients with short disease duration benefit most from TNF antagonist treatment.[5–9] Since axSpA usually affects young persons (for the majority, age of onset lies between mid-20s and early 30s),[1] it has a large impact on work productivity, quality of life, and direct and indirect medical costs.[10–13] Therefore, a diagnostic, and thereby therapeutic, delay is undesirable.

An important explanation for the referral delay in axSpA is that the leading symptom of axSpA, CBP, is very common, especially in primary care.[14 15] Since primary care physicians and other referring specialists may not be sufficiently aware of the disease-specific signs and symptoms which are indicative of axSpA,[16] patients with possible axSpA are not properly distinguished from those with other causes of CBP, resulting in suboptimal referral of these patients.

Over the past decade, several studies have been conducted to develop a referral strategy to aid primary care physicians and medical specialists in the referral of patients with CBP with possible axSpA to the rheumatologist. In each study, the performance and yield of the proposed strategy was assessed. Too unspecific strategies would result in a possible overload of rheumatologist outpatient clinics of patients with non-specific CBP. On the other hand, referral strategies with limited sensitivity would result in a large fraction of patients with axSpA incorrectly *not* referred to the rheumatologist. As of yet, no agreement has been reached regarding which referral strategy would perform best. A recent attempt has been undertaken to compare some of the referral strategies in a cohort of general practice patients, but until now, no study has compared all proposed referral strategies in a single cohort of patients.[17] Therefore, the aim of this study is to evaluate performance of all previously proposed referral strategies by comparing the general characteristics, strengths, limitations and yield of these strategies in patients with CBP referred to the rheumatologist in a single centre.

METHODS

Patients and assessments

Patient data from the SPondyloArthritis Caught Early (SPACE) cohort were used. In this ongoing cohort, patients aged ≥16 years referred to the rheumatology outpatient clinics of five participating centres in Europe with CBP (almost daily; duration ≥3 months but ≤2 years; age of onset <45 years) are included after giving written informed consent. Patients could be referred by general practitioners as well as other specialists such as orthopaedic surgeons, ophthalmologists, gastroenterologists and rheumatologists from other centres. An extensive study description is given elsewhere.[18] The study protocol was approved by the Medical Ethical Committees of the participating centres. All patients gave written informed consent.

At baseline, all patients underwent a protocolled diagnostic workup, including physical examination, assessment of C reactive protein (CRP)/erythrocyte sedimentation rate and human leucocyte antigen (HLA)-B27 status, imaging of the sacroiliac (SI) joints (MRI and plain radiographs) and of SpA features.[19] Rheumatologists were asked to provide a diagnosis based on all collected information, including imaging based on local reading and HLA-B27 status. In addition, rheumatologists were requested to provide a level of confidence about the diagnosis on an 11-point numerical rating scale ranging from 0 (not confident at all) to 10 (very confident). For classification according to the Assessment in SpondyloArthritis international Society (ASAS) axSpA criteria, imaging was evaluated by central readers.[18] If data on SpA features were missing, they were interpreted as being absent. For this study, only data of patients with complete imaging (MRI and plain radiographs of the SI joints) evaluated by central readers from Leiden were used (n=269).

Original and modified referral strategies

The PubMed database was used to identify all previously proposed referral strategies in the literature. Thirteen referral strategies were distilled from the search results and were evaluated in the SPACE cohort.[20–27] The strategies are presented in chronological order based on the date of publication (table 1).

According to the Brandt strategies, patients should be referred to the rheumatologist if HLA-B27+ and/or if they have have inflammatory back pain (IBP).[20] In the original study, it was not indicated how many IBP features should be present in order to classify patients as having IBP. Therefore, we evaluated three versions of the Brandt strategy: in Brandt I, IBP is positive if 1/3 criteria is present, in Brandt II and in Brandt III if 2/3 or 3/3 criteria are present, respectively.

Hermann *et al*[21] showed the potential value of a referral strategy that used Calin's IBP criteria as a single referral parameter.

The performance of the Brandt strategy was evaluated together with a more comprehensive strategy consisting of the Brandt strategy plus two additional parameters: family history for ankylosing spondylitis (AS) and good response to non-steroidal anti-inflammatory drugs (NSAIDs). According to this so-called MASTER strategy, patients should be referred if ≥2/4 features present.[22]

Meanwhile, Braun *et al* proposed the first of two referral studies. This strategy uses five items indicative of IBP as referral parameters (Braun IBP strategy).[23]

An international study called Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) was performed to compare the therein proposed RADAR strategy to the Brandt strategy.[24] The RADAR strategy is similar to the MASTER strategy, but adds extra-articular manifestations (EAM), comprising uveitis/iridocyclitis, psoriasis or inflammatory bowel disease, as the fifth criterion. Also, family history for SpA is used instead of family history for AS. RADAR 2/3 is a simplified strategy proposed by the authors of the RADAR strategy in a post hoc analysis, referring patients if ≥2/3 of the following are present: IBP, good response to NSAIDs, EAM.

The second referral strategy proposed by Braun *et al*,[25] the two-step strategy, is a computer-generated strategy. In the first step of the strategy, presence of psoriasis, bilateral buttock pain and improvement of back pain with

Table 1 Overview of evaluated referral strategies for axSpA

Strategy	IBP	HLA-B27	Good response to NSAIDs	Family history for SpA	Additional criteria	Refer if	IBP definition
Brandt I[20]	+	+	–	–	–	≥1/2 positive	(1) Morning stiffness >30 min (2) Pain at night or in the early morning (3) Improvement of back pain by exercise; IBP positive if ≥1/3 criteria
Brandt II	+	+	–	–	–	≥1/2 positive	See Brandt I IBP positive if ≥2/3 criteria
Brandt III	+	+	–	–	–	≥1/2 positive	See Brandt I IBP positive if ≥3/3 criteria
Hermann[21]	+	–	–	–	–	1/1 positive	Calin's criteria: ≥4/5 of the following: (1) Persistent back pain for ≥3 months (2) Age of onset <40 years (3) Insidious onset of back pain (4) Back pain relieved by exercise (5) Back stiffness especially in the morning
MASTER[22]	+	+	+	+*(AS)	–	≥2/4 positive	(1) Morning stiffness in the lower part of the spine >30 min (2) Improvement by exercise, not by rest (3) Awakening in the night because of back pain, with improvement by exercise
Braun IBP[23]	–	–	+	–	Age at onset CBP≤35 years; waking up in the second half of the night; alternating buttock pain; improvement by movement, not rest	≥2/5 positive	NA
RADAR[24]	+	+	+	+	Extra-articular manifestations†	≥2/5 positive	By referring physician's opinion (ie, any set of criteria)
RADAR 2/3	+	–	+	–	Extra-articular manifestations	≥2/3 positive	See RADAR
Braun two-step[25]	–	(+)	–	–	Psoriasis; buttock pain; improvement of back pain by exercise (only if ≤1/3 positive, HLA-B27 is tested)	≥2/3 or HLA-B27+	NA
Braun two-step alt.	–	(+)	–	–	Psoriasis; alternating buttock pain; improvement of back pain by exercise (only if ≤1/3 positive, HLA-B27 is tested)	≥2/3 or HLA-B27+	NA

Continued

Table 1 Continued

Strategy	IBP	HLA-B27	Good response to NSAIDs	Family history for SpA	Additional criteria	Refer if	IBP definition
CaFaSpA ≥1pt[26]	+	–	+	+	–	≥1/3 positive	ASAS criteria: ≥4/5 of the following: (1) Age at onset <40 years (2) Insidious onset (3) Improvement with exercise (4) No improvement with rest (5) Pain at night (with improvement on getting up)
CaFaSpA ≥2pt	+	–	+	+	–	≥1/3 positive	See CaFaSpA ≥1pt
ASAS[27]	+	+	+	+	Peripheral manifestations;‡ extra-articular manifestations; elevated acute phase reactants§	≥1/7 positive	See CaFaSpA ≥1pt

*In the MASTER strategy, positive family history for AS, not SpA, is used as a referral parameter.
†Extra-articular manifestations: uveitis, psoriasis and/or IBD.
‡Peripheral manifestations: arthritis, enthesitis and/or dactylitis.
§Acute phase reactants, CRP and/or ESR.
alt, alternative; AS, ankylosing spondylitis; ASAS, Assessment in SpondyloArthritis international Society; CBP, chronic back pain; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; IBP, inflammatory back pain; NA, not available; NSAIDs, non-steroidal anti-inflammatory drugs; RADAR, Recognising and Diagnosing Ankylosing Spondylitis Reliably; SpA, spondyloarthritis.

exercise are registered. Patients are referred if ≥2 features are present. If ≤1 feature is present, HLA-B27 is tested in a second step; only HLA-B27+ patients are referred. Since alternating buttock pain is more specific for SpA than bilateral buttock pain,[23] we also analysed a slight alteration of the Braun two-step strategy in which we used alternating buttock pain as a criterion instead of bilateral buttock pain.

In the Case Finding Axiale Spondylarthropathie (CaFaSpA) strategy, a good response to NSAIDs, positive family history for SpA and IBP are all awarded 1 point; disease duration ≥5 years is awarded 0.5 point; patients with ≥1.5 points should be referred. However, owing to the inclusion criteria of the SPACE cohort (disease duration of ≤2 years), it was not possible to evaluate the latter criterion and therefore, it was omitted from the strategy. Instead, two separate cut-off levels were evaluated: ≥1 and ≥2 points.

Most recently, ASAS published referral recommendations. According to these recommendations, patients should be referred if ≥1 SpA feature is present in patients with CBP (duration ≥3 months) with back pain onset ≤45 years.[27]

Imaging was omitted from all strategies as it was never recommended in the referral strategies to perform imaging for screening purposes only, but it could be used when an imaging result was coincidentally available. In the SPACE cohort, however, imaging data are collected for *all* patients as part of the study protocol. Leaving imaging in the referral strategies would overestimate performance of the strategies. Moreover, imaging, and in particular MRI, is not likely to be feasible for screening purposes due to the high costs and the skill required to interpret imaging correctly.[10] The Brandt (any imaging modality, not further specified), MASTER (radiographs, MRI, CT and/or scintigraphy), RADAR (not further specified) and ASAS (radiographs and/or MRI) strategies are therefore modified by omitting imaging from the original strategies.

Since different definitions were used for IBP, those definitions are highlighted in table 1. For this study, the ASAS definition for IBP was used (except for the Brandt and Hermann strategies), as recommended by ASAS.[27]

Data analysis

The performance of the strategies was evaluated by calculating sensitivity, specificity and positive likelihood ratio (LR+), using primarily diagnosis by the rheumatologist as the external standard. In additional analyses, classification according to the ASAS axSpA criteria was used as the external standard.[19] For each erroneously referred patient (ie, patients *not* fulfilling the ASAS criteria but who are referred, the so-called 'false-positive' (FP) patients), post-test probability for axSpA was calculated based on the LR product for presence of SpA features.[28] A pretest probability of 5% was assumed.[29] By converting this pretest probability into pretest odds, and by multiplying it with the LR product of present SpA

features,[28] post-test probabilities were calculated. An LR product ≥78 (equalling a post-test probability ≥80%) was used as the cut-off value for probable axSpA. For the erroneously not referred patients (ie, patients fulfilling the ASAS criteria but who are *not* referred, the so-called 'false-negative' (FN) patients), it was evaluated which ASAS criteria arm (ie, clinical arm, imaging arm or both arms) they fulfilled. For these analyses, SPSS Statistics V.22.0 was used.

We primarily evaluated performance of referral strategies using the final diagnosis by the rheumatologist as the external standard (which is based on a local reading of the imaging), as this would most reflect the clinical setting in which referral strategies are aimed to be used. However, we also evaluated performance of referral strategies by using the ASAS axSpA criteria as the external standard as this allowed us to calculate post-test probabilities based on centrally scored imaging and gave a better insight into the characteristics of patients that would have been referred or not referred.

RESULTS

Patient characteristics

Data on diagnosis were available for 261/269 patients (97%), 107 (41%) of whom were diagnosed with axSpA (table 2). The mean age at inclusion was 31.0 (SD 8.8) years; 86/261 (33%) of the patients were male; 79 (30%) were HLA-B27+ (table 2). In total, 79/261 (30%) patients fulfilled the ASAS criteria (table 2); 37/79 (47%) fulfilled the imaging arm (with or without the clinical arm) of the ASAS criteria of whom 20 had radiographic sacroiliitis using central reading and 42/79 (53%) fulfilled the clinical arm only.

Performance of the strategies

All 107 patients with axSpA were referred at least once; of the patients without axSpA, most patients (147/154; 95%) were referred at least once.

The ASAS and Brandt I strategies were the most sensitive strategies (sensitivity 98%), but have a low specificity (18% and 11%, respectively), resulting in an LR+ of

Table 2 Baseline characteristics of patients with chronic back pain included in the Leiden SPACE cohort

	All patients (n=261)	Patients diagnosed with axSpA (n=107)	Patients not diagnosed with axSpA (n=154)
Demographical and back pain characteristics			
Age at inclusion, mean (SD), in years	31.0 (8.8)	30.4 (8.3)	31.4 (9.2)
Male, n (%)	86 (33.0%)	43 (40.2%)	43 (27.9%)
Duration of back pain, mean (SD), in months	13.4 (7.3)	13.1 (7.2)	13.7 (7.5)
Age at onset <40 years, n (%)	217 (83.1%)	90 (84.1%)	127 (82.5%)
Certainty of diagnosis, mean (SD)	7.1 (2.4)	7.2 (2.5)	7.0 (2.2)
Fulfilling ASAS axSpA criteria, n (%)	79 (30.3%)	63 (58.9%)	16 (10.4%)
SpA features			
HLA-B27+, n (%)	79 (30.3%)	57 (53.3%)	22 (14.3%)
Positive family history of SpA, n (%)	95 (36.4%)	50 (46.7%)	45 (29.2%)
Psoriasis, n (%)	25 (9.6%)	14 (13.1%)	11 (7.1%)
Dactylitis, n (%)	8 (3.1%)	7 (6.5%)	1 (0.6%)
Enthesitis, n (%)	25 (9.6%)	20 (18.7%)	5 (3.2%)
Uveitis, n (%)	17 (6.5%)	13 (12.1%)	4 (2.6%)
IBD, n (%)	19 (7.3%)	10 (9.3%)	9 (5.8%)
CRP (mg/L), mean (SD)	6.9 (11.1)	9.8 (15.3)	4.9 (6.1)
ESR (mm/hour), mean (SD)	10.5 (12.0)	14.2 (16.3)	8.1 (7.1)
Elevated CRP/ESR, n (%)	45 (17.2%)	28 (26.2%)	17 (11.0%)
Good response to NSAIDs, n (%)	69 (26.4%)	36 (33.6%)	33 (21.4%)
Sacroiliitis on radiographs, n (%)	22 (8.4%)	16 (15.0%)	6 (3.9%)
Sacroiliitis on MRI, n (%)	27 (10.3%)	26 (24.3%)	1 (0.6%)
IBP* (ASAS), n (%)	152 (58.2%)	78 (72.9%)	74 (48.1%)
Inflammatory back pain features			
Improvement of back pain by rest, n (%)	60 (23.0%)	24 (22.4%)	36 (23.4%)
Improvement of back pain by exercise, n (%)	164 (62.8%)	79 (73.8%)	85 (55.2%)
Buttock pain, n (%)	128 (49.0%)	60 (56.1%)	68 (44.2%)
Alternating buttock pain, n (%)	67 (25.7%)	25 (23.4%)	42 (27.3%)
Night pain, n (%)	164 (62.8%)	71 (66.4%)	93 (60.4%)
Pain in second half of night, n (%)	78 (29.9%)	35 (32.7%)	43 (27.9%)
Insidious onset, n (%)	228 (87.4%)	95 (88.8%)	133 (86.4%)
Morning stiffness, n (%)	199 (76.2%)	88 (82.2%)	111 (72.1%)

*IBP definition by ASAS criteria.[35]
ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IBD, inflammatory bowel disease (Crohn's disease/ulcerative colitis); IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SPACE, SPondyloArthritis Caught Early.

1.2 and 1.1, respectively (table 3). RADAR 2/3 was the most specific strategy (specificity 82%). The MASTER strategy had the most balanced sensitivity (64%) and specificity (76%) and therefore the highest LR+ (2.68; table 3).

Eighteen (17%) of the 107 patients diagnosed with axSpA would correctly have been referred by all 13 strategies. Fourteen of these patients have IBP, which is included in 10 of the 13 referral strategies as a referral parameter; in the other 3 strategies, features indicative of IBP are included.

Performance of the strategies using classification as the external standard

When using classification by ASAS axSpA criteria as the external standard, the ASAS strategy and the Brandt I strategy are the only referral strategies that would have referred all patients fulfilling the ASAS criteria (sensitivity 100%), but have a low specificity (16% and 10%, respectively) resulting in an LR+ of 1.2 and 1.1, respectively. All other strategies have a lower sensitivity, yet higher specificity (table 4). Out of the 13 referral strategies, the Braun two-step alternative (alt.) strategy has the most balanced sensitivity (86%) and specificity (73%) and therefore the highest LR+ (3.1).

Of the 79 patients fulfilling the ASAS criteria, 18 (23%) would correctly have been referred by all referral strategies. These 18 patients all fulfil the clinical arm of the ASAS criteria; 5 also fulfil the imaging arm (2 with radiographic sacroiliitis). All 18 patients have IBP, which is included in 10 of the 13 referral strategies as a referral parameter; in the other 3 strategies, features indicative of IBP are included.

Most referral strategies would have referred all 42 patients who fulfill the clinical arm of the ASAS criteria only. Only the Hermann, Braun IBP, RADAR 2/3 and CaFaSpA ≥2pt strategies would miss some of these patients, as these strategies do not include HLA-B27 as a referral parameter.

Patients with axSpA missed by the strategies using classification as the external standard

In total, 61/79 (77%) patients who fulfilled the ASAS axSpA criteria would not have been referred by ≥1 different strategies despite fulfilling the ASAS criteria (FN patients; table 5). Twenty-seven of these 61 FN patients would have been missed by only one strategy, the majority (19 patients) only by the RADAR 2/3 strategy. Twelve of the 61 FN patients would have been missed by two different strategies. Most of these 12 patients would have been missed by the RADAR 2/3 strategy (10/12 patients) and the CaFaSpA ≥2pt strategy (7/12 patients).

Twenty-two out of the 61 FN patients would have been missed by ≥3 different strategies, of whom 18 fulfilled the imaging arm of the ASAS criteria (11 with radiographic sacroiliitis). These 22 FN patients have 1–6 SpA features (see online supplementary table). Seven of these 22 FN patients have positive imaging and only one other SpA feature; these patients would therefore have been missed frequently (by 6–11 referral strategies, depending on the presence of the specific SpA feature in a patient). The remaining 15 FN patients show a very

Table 3 Performance of the referral strategies in the Leiden SPACE cohort using diagnosis by the rheumatologist as the external standard

107 diagnosed with axSpA 154 not diagnosed with axSpA		Correctly referred/correctly *not* referred patients			
		Patients diagnosed with axSpA by the rheumatologist referred by strategies (correctly referred)		Patients *not* diagnosed with axSpA by the rheumatologist *not* referred by strategies (correctly *not* referred)	
Strategy	**LR+**	**N out of 107**	**Sensitivity**	**N out of 154**	**Specificity**
Brandt I	1.10	105	0.98	17	0.11
Brandt II	1.23	99	0.93	38	0.25
Brandt III	1.86	79	0.74	93	0.60
Hermann	1.19	89	0.83	46	0.30
MASTER	2.68	69	0.64	117	0.76
Braun IBP	1.29	84	0.79	60	0.39
RADAR	2.12	84	0.79	97	0.63
RADAR 2/3	2.51	47	0.44	127	0.82
Braun two-step	1.83	80	0.75	91	0.59
Braun two-step alt.	2.10	70	0.65	106	0.69
CaFaSpA ≥1pt	1.25	93	0.87	47	0.31
CaFaSpA ≥2pt	1.98	55	0.51	114	0.74
ASAS	1.20	105	0.98	28	0.18

alt, alternative; ASAS, Assessment in SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IBP, inflammatory back pain; LR+, positive likelihood ratio; RADAR, Recognising and Diagnosing Ankylosing Spondylitis Reliably; SPACE, Spondyloarthritis Caught Early.

Table 4 Performance of the referral strategies in the Leiden SPACE cohort using classification by ASAS axSpA criteria as the external standard

79 fulfilling the ASAS criteria 182 not fulfilling the ASAS criteria		Correctly referred/correctly not referred patients			
		Patients fulfilling the ASAS criteria referred by strategies (correctly referred)		Patients *not* fulfilling the ASAS criteria *not* referred by strategies (correctly *not* referred)	
Strategy	**LR+**	**N out of 79**	**Sensitivity**	**N out of 182**	**Specificity**
Brandt I	1.12	79	1.00	19	0.10
Brandt II	1.29	77	0.97	44	0.24
Brandt III	2.37	71	0.90	113	0.62
Hermann	1.19	67	0.85	52	0.29
MASTER	3.00	60	0.76	136	0.75
Braun IBP	1.33	65	0.82	69	0.38
RADAR	2.34	71	0.90	112	0.62
RADAR 2/3	1.66	31	0.39	139	0.76
Braun two-step	2.27	71	0.90	110	0.60
Braun two-step alt.	3.13	68	0.86	132	0.73
CaFaSpA ≥1pt	1.35	74	0.94	56	0.31
CaFaSpA ≥2pt	2.35	47	0.61	135	0.74
ASAS	1.20	79	1.00	30	0.16

alt, alternative; ASAS, Assessment in SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IBP, inflammatory back pain; LR+, positive likelihood ratio; RADAR, Recognising and Diagnosing Ankylosing Spondylitis Reliably; SPACE, Spondyloarthritis Caught Early.

Table 5 Overview of incorrectly referred/incorrectly not referred patients with chronic back pain by the referral strategies using classification by the ASAS axSpA criteria as the external standard

	Incorrectly referred/incorrectly not referred patients					
			Incorrectly *not* referred (ie, FN) patients†			
	Incorrectly referred (ie, FP) patients*			Fulfilling imaging arm		
Strategy	**N**	**With PTP≥80% axSpA N (% of total FP patients)**	**N (%) out of 79**	**Radiographic sacroiliitis**	**Sacroiliitis on MRI only**	**Fulfilling clinical arm only**
Brandt I	163	8 (5%)	0 (0%)	–	–	–
Brandt II	138	8 (6%)	2 (3%)	1	1	–
Brandt III	69	7 (10%)	8 (10%)	4	4	–
Hermann	130	7 (5%)	12 (15%)	5	3	4
MASTER	46	7 (15%)	19 (24%)	11	7	1
Braun IBP	113	8 (7%)	14 (18%)	3	4	7
RADAR	70	7 (10%)	8 (10%)	6	2	–
RADAR 2/3	43	4 (9%)	48 (61%)	12	11	25
Braun two-step	72	8 (11%)	8 (10%)	3	5	–
Braun two-step alt.	50	7 (14%)	11 (14%)	4	7	–
CaFaSpA ≥1pt	126	7 (6%)	5 (6%)	2	3	–
CaFaSpA ≥2pt	47	4 (9%)	31 (39%)	14	10	7
ASAS	152	8 (5%)	0 (0%)	–	–	–

*FP patients are patients *not* fulfilling the axSpA criteria who are referred by the strategies.
†FN patients are patients fulfilling the axSpA criteria who are *not* referred by the strategies.
alt, alternative; ASAS, Assessment in SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IBP, inflammatory back pain; FN, false-negative; FP, false-positive; PTP, post-test probability; RADAR, Recognising and Diagnosing Ankylosing Spondylitis Reliably.

heterogeneous presentation of the disease and therefore, it is not possible to recognise a pattern of SpA features or types of patients who would have been missed by a specific referral strategy.

In general, most of the FN patients fulfil the imaging arm of the ASAS criteria; 2 (5%) to 24 (65%) of the 37 patients fulfilling the imaging arm criteria would have been missed (by the Brandt II and the CaFaSpA ≥2pt strategy, respectively; table 5). Of these FN patients fulfilling the imaging arm, 36–75% (depending on the strategy) have radiographic sacroiliitis.

Patients without axSpA referred by the strategies using classification as the external standard

Another characteristic that the strategies have in common is that many patients (43–163 patients, depending on the strategy) not fulfilling the ASAS criteria would have been referred (FP patients; table 5), resulting in specificities of only 10% (Brandt I) to 76% (RADAR 2/3; table 4). Only 7/182 (4%) patients without axSpA would not have been referred by any strategy; 64 (35%) would have been referred by 1–5 strategies; 76 (42%) by 6–10 strategies and 35 (19%) by 10–13 strategies. Six of these 182 patients would have been referred by every referral strategy as all 6 had IBP (ASAS definition) as well as morning stiffness, and 5/6 also had bilateral and alternating buttock pain.

On the other hand, up to eight FP patients have a post-test probability ≥80% for axSpA and would arguably have been referred correctly despite not fulfilling the ASAS criteria. Of these eight FP patients, four were HLA-B27+, had alternating buttock pain (which is an SpA feature but not included in the ASAS criteria) and one additional SpA feature (three patients had a positive family history for SpA, one had enthesitis). The four HLA-B27− patients had 4–6 SpA features. All four had a positive family history for SpA, IBP and a good response to NSAIDs; three also had psoriasis.

DISCUSSION

In this study, 13 referral strategies for axSpA were compared in a single cohort of patients for the first time. Since most strategies performed reasonably well in the SPACE cohort, the potential value of referral strategies is clearly shown. However, all strategies have disadvantages that need to be assessed in order to provide an optimal referral strategy for use in daily clinical practice.

To be of use in the daily clinical setting, referral strategies should provide an optimal yield of patients subsequently being diagnosed with axSpA after referral and must also be easily applicable. Referral strategies should not take a lot of time to perform or have too many referral parameters, and should not rely too much on subjective matters and/or clinical parameters that require training and experience to assess properly.[10] In addition, an ideal referral strategy should be as inexpensive as possible, because CBP is very common, especially in primary care.[14 15]

We omitted imaging as a referral parameter if used in the original studies, as it is unfeasible for screening purposes in most countries due to the costs (especially for MRI), radiation exposure (only for radiographs) and interpretation difficulties (especially for pelvic radiographs).[30–32] In countries with a different healthcare structure where it is more common to have imaging available in primary care, such as Germany,[10] imaging data could be of use in referral of patients to the rheumatologist if coincidentally available, although the difficulties in interpretation will remain. This indicates that an optimal referral strategy might be different in different countries.

HLA-B27 as a screening parameter is appealing as it is easy to interpret (either present or absent), but the value of HLA-B27 for screening is, among others, dependent on its prevalence in the general population,[33] which varies widely geographically and ethnically.[34]

IBP also seems appealing as a screening parameter as it is regarded as the leading clinical symptom of axSpA. However, there is increasing evidence that IBP is only present in ~70–80% of patients with axSpA.[28 35 36] Moreover, it is not easy for an untrained physician to assess the presence/absence of IBP.[10] Studies show a poor agreement between referring physicians and rheumatologists for IBP, as well as regarding many other referral parameters.[22 37]

In this perspective, the Braun two-step strategy (either with bilateral or alternating buttock pain), for example, is easily applicable because the assessed parameters are not too difficult to ask of an untrained physician, non-invasive (as no imaging is performed) with relatively low costs, due to the fact that HLA-B27 testing is only required in ~50% of patients.[25] Yet some patients with axSpA will be missed by this strategy, as is the case with most other strategies too.

The patients with axSpA missed by the referral strategies predominantly fulfil the imaging arm of the ASAS criteria. Even the best performing referral strategy (using the ASAS axSpA criteria as an external standard), in terms of best balanced sensitivity and specificity (ie, the Braun two-step alt. strategy), would have missed 11/38 (29%) patients fulfilling the imaging arm. Also, a large fraction (21–50%) of patients fulfilling the ASAS criteria with elevated CRP would have been missed by several strategies (data not shown). Given the fact that shorter disease duration also positively correlates with treatment response and longer duration is associated with worse outcomes,[5–9 38] it is vital to implement a referral strategy that can identify as many of these patients as early as possible, especially in a primary care setting. Therefore, including disease duration ≥5 years as a referral parameter, as in the original CaFaSpA strategy,[26] seems undesirable.

When comparing SpA features of the patients with axSpA missed by the referral strategies, it becomes clear that they constitute a heterogeneous population. Therefore, it is impossible to pin out certain SpA features that should always be included in a referral strategy or SpA features that can easily be omitted. The current analysis by classification suggests that it is only possible to not miss a single patient with axSpA by using all SpA features as referral parameters, such as ASAS has proposed in their referral strategy.[27] However, one should take into account that in this analysis the external standard (ASAS axSpA criteria) and the referral parameters (ASAS-defined SpA features) are composed of the same features, so by definition anyone meeting the ASAS

criteria has an ASAS-defined SpA feature. Also, for implementing the ASAS strategy correctly, knowledge of the wide range of SpA features is necessary and determining the presence or absence of certain SpA features can be problematic for non-specialists. Moreover, by choosing a very sensitive, yet unspecific, referral strategy such as the ASAS strategy, rheumatologists might have to see many patients to make the diagnosis in one patient (ie, the positive predictive value of the strategy is low). If the healthcare system can facilitate this, the ASAS strategy would be the ideal strategy.[39] Our findings are confirmed by a study by van Hoeven and colleagues showing similar results regarding the ASAS referral strategy in the primary care setting: sensitivity 100%, specificity 22%, LR+ 1.28. Since imaging was not omitted in the strategies they investigated, the Brandt, MASTER and RADAR studies had almost perfect sensitivity, as is to be expected when adding imaging in a referral strategy, and are thus incomparable to our results.

Besides the quest for an ideal referral strategy, educating primary care physicians and referring specialists is likely to be essential for early referral of patients with CBP.[40] This is especially important if the comprehensive ASAS strategy is to be implemented in daily practice. Additionally, increasing awareness of the disease can significantly increase the number of axSpA referrals.[41] The relatively high percentage of axSpA diagnoses among referred patients in the original prospective referral strategy studies (ranging from 33% in the Hermann study to 45.4% in the Brandt study)[20–25] might be a reflection of the raised awareness of physicians for axSpA during these referral studies.[25 42] However, it remains unknown how many patients with possible axSpA were incorrectly not referred as only referred patients underwent a complete diagnostic procedure.

A major limitation of our study is that the patients in the SPACE cohort are already referred to a rheumatologist, probably causing an overestimation of all strategies. However, neither sensitivity, specificity nor LR+, which we specifically chose as parameters to evaluate the performance of the referral strategies, is contingent on the pretest probability of having axSpA, which is higher in the SPACE cohort (30.8%)[18] as compared with the primary care setting (estimated at 5%). Moreover, in our secondary analysis, we used fulfilment of the ASAS criteria rather than the final diagnosis by the rheumatologist as the outcome. Fulfilment of ASAS criteria is highly correlated to diagnosis by the rheumatologist, as is shown by ASAS as well as in our cohort, and is therefore a reasonable proxy for diagnosis by the rheumatologist.[18 19] Fulfilment of ASAS criteria is less likely to be affected by interpretation limitations, improving the external validity of this study. In particular, this allowed us to use centrally scored imaging data with two central readers, which reduces misclassification.[31 32] Moreover using the ASAS criteria provides more detailed knowledge on the type of patient correctly or incorrectly referred by a given strategy.

In summary, many referral strategies performed reasonably well in the SPACE cohort, although all strategies had specific limitations. If the goal is to not miss any patient with axSpA, the ASAS strategy could be the strategy of choice. If a more stringent approach is preferred, aimed at constraining the amount of referrals for instance, the MASTER strategy could be used. The 'ideal' referral strategy may be different from country to country, due to differences in the healthcare structure and prevalence of referral parameters such as HLA-B27. Proper education of primary care physicians and medical specialists could further augment the value of referral strategies. Further (prospective) research should be conducted to show the true merits of referral strategies in daily practice.

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