Raising the bar for classification and outcome assessment for clinical studies in axial spondyloarthritis

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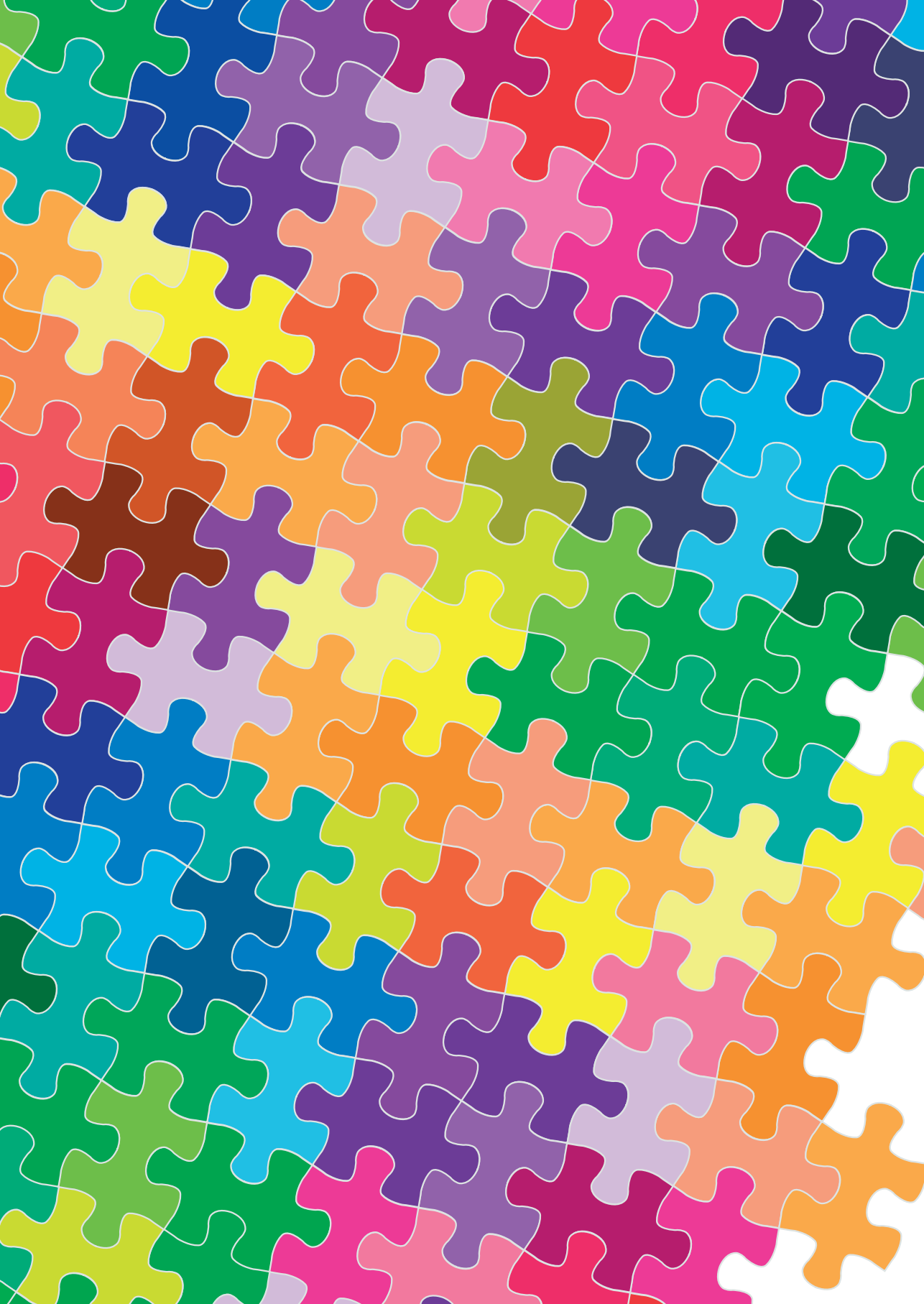

PART I

AXIAL SPONDYLOARTHRITIS DISEASE CHARACTERISTICS

CHAPTER 2

DO PATIENTS WITH AXIAL SPONDYLOARTHRITIS WITH RADIOGRAPHIC SACROILIITIS FULFIL BOTH THE MODIFIED NEW YORK CRITERIA AND THE ASAS AXIAL SPONDYLOARTHRITIS CRITERIA? RESULTS FROM EIGHT COHORTS.

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ABSTRACT

Background

Patients with spondyloarthritis with radiographic sacroiliitis are traditionally classified according to the modified New York (mNY) criteria as ankylosing spondylitis (AS) and more recently according to the Assessment of SpondyloArthritis international Society (ASAS) criteria as radiographic axial spondyloarthritis (r-axSpA).

Objective

To investigate the agreement between the mNY criteria for AS and the ASAS criteria for r-axSpA and reasons for disagreement.

Methods

Patients with back pain ≥3 months, diagnosed as axSpA with radiographic sacroiliitis (mNY radiographic criterion) were selected from eight cohorts (ASAS, Esperanza, GESPIC, OASIS, Reuma.pt, SCQM, SPACE, UCSF). Subsequently, we calculated the percentage of patients who fulfilled the ASAS r-axSpA criteria within the group of patients who fulfilled the mNY criteria, and vice- versa in six cohorts with complete information.

Results

Of the 3882 patients fulfilling the mNY criteria, 93% also fulfilled the ASAS r-axSpA criteria. Inversely, of the 3434 patients fulfilling the ASAS r-axSpA criteria, 96% also fulfilled the mNY criteria. The main cause for discrepancy between the two criteria sets was the reported age at onset of back pain.

Conclusion

Almost all patients with axSpA with radiographic sacroiliitis fulfil both ASAS and mNY criteria, which supports the interchangeable use of the terms AS and r-axSpA.

INTRODUCTION

Traditionally, patients with axial spondyloarthritis (axSpA) with definite structural changes on conventional radiographs are classified according to the modified New York (mNY) criteria as ankylosing spondylitis (AS). However, they may also be classified according to the more recent Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria as radiographic axSpA (r-axSpA).

Both the mNY and the ASAS axSpA classification criteria use the radiographic criterion as defined by the mNY criteria (ie, sacroiliitis of at least grade 2 bilaterally or at least grade 3 unilaterally). However, the additionally required (clinical) features of the classification criteria differ (table 1). Importantly, patients with age at onset of back pain ≥45 years cannot fulfil the ASAS criteria, but there is no age limit for the mNY criteria.[1,2] Patients without the inflammatory character of back pain fulfil the ASAS criteria if another SpA feature is present, but only fulfil the mNY criteria if there is limitation in spinal mobility. These differences in the clinical part of both criteria sets raise the question whether the two sets classify the same patients with axSpA with radiographic sacroiliitis.

The aim of this study was to investigate if patients who fulfil the mNY criteria also fulfil the ASAS criteria for r-axSpA and vice- versa. The second objective was to investigate reasons for disagreement.

METHODS

Patients diagnosed with axSpA who had back pain for at least 3 months and definite radiographic sacroiliitis based on local reading, according the mNY radiographic criterion (#4a or 4b in table 1) were selected from eight cohorts (ASAS, Esperanza, GErman SPondyloarthritis Inception Cohort (GESPIC), Outcome in Ankylosing Spondylitis International Study (OASIS), Reuma.pt, Swiss Clinical Quality Management (SCQM), SPondyloArthritis Caught Early cohort (SPACE), and University of California San Francisco (UCSF) axSpA cohort[1,3–9]). The ASAS cohort included patients with undiagnosed axSpA irrespective of symptom duration, in 25 ASAS centres across 16 countries in Western-Europe, Turkey, Asia, Colombia and Canada between 2005 and 2009.[1] Esperanza is a Spanish national health programme for early SpA, which started inclusion in 2007.[6] GESPIC started in 2000 and consists of patients with axSpA and symptom duration of up to 10 years.[7] OASIS consists of Dutch, Belgian and French patients with established AS, which started in 1996.[8]

Table 1 Classification of axial spondyloarthritis with radiographic sacroiliitis using the mNY criteria for the classification of AS[17], and the ASAS criteria for the classification of r-axSpA[1].

mNY criteria for the classification of AS	**ASAS criteria** for the classification of radiographic axSpA
1. Low back pain and stiffness for at least 3 months, which improves with exercise and is not relieved by rest 2. Limitation of lumbar spine motion in the sagittal and frontal planes 3. Decreased chest expansion, compared to age- and sex-matched controls **4a**. Unilateral sacroiliitis grade 3 or 4 **4b**. Bilateral sacroiliitis grade 2 to 4	1. Back pain ≥3 months 2. Age at onset <45 years 3. Definite radiographic sacroiliitis according to mNY criteria 4. ≥1 SpA feature: – Inflammatory back pain – Arthritis – Enthesitis – Uveitis – Dactylitis – Psoriasis – Crohn's/colitis – Good response to NSAIDs – Family history for SpA – HLA-B27 positive – Elevated CRP (or ESR)
Definite AS if sacroiliitis as described in 4a or 4b and any of the clinical symptoms (1-3)	Definite r-axSpA if fulfilment of 1 and 2, sacroiliitis as described in 3 and at least one of the clinical SpA features as described in 4

AS, Ankylosing Spondylitis; ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial Spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, Human leukocyte antigen B27; mNY, modified New York; NSAID, nonsteroidal anti-inflammatory drugs; r-axSpA, radiographic axial spondyloarthritis

Since 2008, Reuma.pt started with the inclusion of Portuguese rheumatic patients of various diseases and disease stages in a national register; including patients with early and established axSpA.[3] The SCQM axSpA cohort started in Switzerland in 2005 including patients with early and established disease.[4] SPACE is an early chronic back pain cohort including European patients since 2009.[9] Patients in the UCSF axSpA cohort started enrolling in 2007; patients with early and established disease from the UCSF clinic are included.[5] Approval from the medical ethical committees was obtained per cohort, and for all patients written informed consent was obtained prior to inclusion.

For these cohorts, we calculated how many patients with SpA with radiographic sacroiliitis fulfil the mNY criteria (mNY+) and the ASAS r-axSpA criteria (ASAS+). Subsequently, we calculated the percentage of patients who fulfil the ASAS r-axSpA criteria within the group of patients who fulfil the mNY criteria. In six cohorts, we were also able to calculate the percentage of patients fulfilling the mNY criteria within the group fulfilling the ASAS r-axSpA criteria. For the Esperanza and OASIS cohorts, specific information on the individual items of the mNY clinical criteria was unavailable. Consequently, it was not possible to calculate the percentage of patients fulfilling the mNY criteria within the subgroup fulfilling the ASAS criteria. Flowcharts were used to visualise fulfilment of the criteria sets (online supplementary figure S1).

For the patients with axSpA with radiographic sacroiliitis, the first step was to determine whether a patient had inflammatory back pain (IBP). For the purpose of this study, the first clinical criterion of the mNY was equated to IBP according to the ASAS definition.[10] The second step was to determine the number of SpA features (<1 vs ≥1) as well as whether the patient had mobility restrictions. Mobility restrictions were defined using the age-adjusted fifth percentile scores of healthy individuals from Ramiro *et al*.[11] ; if the Schober's test and lateral spinal flexion were below the age-adjusted fifth percentile value or chest expansion was below the age-adjusted and height-adjusted fifth percentile value, mobility was considered restricted. The final step was to look at age at onset of back pain (<45 vs ≥45 years old).

RESULTS

A total of 7636 patients with a SpA diagnosis and back pain >3 months were included in these eight cohorts. Of these, 4041 patients had a diagnosis of axSpA with radiographic sacroiliitis and were available for analysis. In total, 3882 patients fulfilled the mNY criteria, of which 3607 (93%; range 88%–100%) also fulfilled the ASAS r-axSpA criteria (figure 1A). From the six cohorts (n=3721) in which the fulfilment of the mNY criteria in the subgroup of patients fulfilling the ASAS r-axSpA criteria (n=3434) could be analysed, 3300 (96%; range 84%–98%) also fulfilled the mNY criteria (figure 1B).

For all, 4041 patients with r-axSpA fulfilment of the criteria sets was determined (online supplementary tables S1-S3). In total, 3607 (89%) of patients fulfilled both criteria sets; 275 (7%) only the mNY criteria; 134 (3%) only the ASAS criteria and 25 (1%) neither set (table 2).

Table 2 Percentage of patients with axSpA with radiographic sacroiliitis fulfilling both sets of criteria, either criteria set or neither

	mNY+ ASAS+	mNY+ ASAS-	mNY- ASAS+	mNY- ASAS-	Total mNY+*	Total ASAS+ǂ
ASAS (n=114)	86% (98)	2% (3)	10% (11)	2% (2)	89% (101)	96% (109)
GESPIC (n=96)	81% (78)	12% (11)	6% (6)	1% (1)	93% (89)	88% (84)
Esperanza (n=109)	97% (106)	3% (3)	NA‡	NA‡	100% (109)	--
OASIS (n=211)	95% (201)	5% (10)	NA‡	NA‡	100% (211)	--
Reuma.pt (n=1320)	88% (1156)	7% (93)	4% (55)	1% (16)	95% (1249)	92% (1211)
SCQM (n=1806)	89% (1612)	8% (148)	2% (40)	0.3% (6)	97% (1760)	91% (1652)
SPACE (n=92)	84% (77)	0% (0)	16% (15)	0% (0)	84% (77)	100% (92)
UCSF (n=293)	95% (279)	2.5% (7)	2.5% (7)	0% (0)	98% (286)	98% (286)
Total (n=4041)	89% (3607)	7% (275)	3% (134)	1% (25)	96% (3882)	--

*The total percentage of patients who fulfil the mNY criteria per cohort and in total; ǂ The total percentage of patients who fulfil the ASAS r-axSpA criteria per cohort and in total.‡ Specific information on the individual items of the mNY clinical criteria was unavailable, it was therefore not possible to accurately calculate the number of patients fulfilling the mNY in the subgroup fulfilling the ASAS r-axSpA criteria. ASAS, Assessment of SpondyloArthritis international Society cohort; Esperanza, Spanish national health programme for early SpA; GESPIC, GErman SPondyloarthritis Inception Cohort; NA, not available; OASIS, Outcome in Ankylosing Spondylitis International Study; Reuma.pt, Portuguese Register for Rheumatic Diseases; SCQM, Swiss Clinical Quality Managementcohort; SPACE, SPondyloArthritis Caught Early cohort; UCSF, University of California San Francisco axSpA cohort; axSpA, axial spondyloarthritis; mNY, modified New York; r-axSpA, radiographic axial spondyloarthritis

The main difference between the two criteria sets was caused by the reported age at onset of back pain; 99.7% of the patients fulfilling the mNY criteria could potentially fulfil the ASAS criteria except for registered age at onset (online supplementary figure S4).

Out of the 275 mNY +patients not fulfilling the ASAS criteria (7% of all included patients), 265 (96%) cases were due to the age criterion and 10 (4%) due to the absence of SpA features including IBP (online supplementary table 1). These 10 patients had spinal mobility limitation as the only clinical feature. The 134 mNY-/ASAS+ did not have mobility restriction or IBP but another SpA feature instead.

For the cohorts that had data available (n=1833), the human leucocyte antigen B27 (HLA-B27) status was determined in each of the subgroups. In the mNY+/ASAS+ group, HLA-B27 positivity was 68%. In the mNY-/ASAS+ group, a similar percentage was found (72%), whereas in the mNY+/ASAS- group this percentage was only 46%, thus only slightly higher than the mNY-/ASAS- group (42%) (online supplementary table S2).

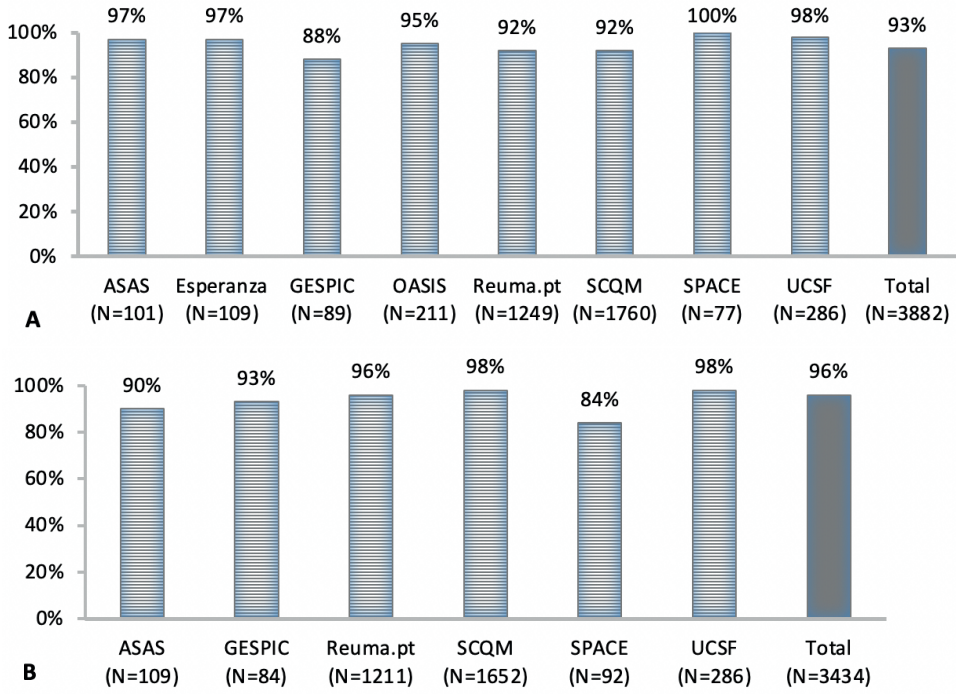

Figure 1: Percentage of patients fulfilling ASAS r-axSpA within subgroup fulfilling mNY criteria (3607/3882) (A) and percentage of patients fulfilling mNY criteria within subgroup fulfilling ASAS r-axSpA (3300/3434) (B), per cohort and overall.
ASAS, (Assessment of SpondyloArthritis international Society cohort); Esperanza, Spanish national health programme for early SpA; Esperanza (Spanish national health programme for early SpA); GESPIC, (GErman SPondyloarthritis Inception Cohort); mNY, modified New York; OASIS, (Outcome in Ankylosing Spondylitis International Study); r-axSpA, radiographic axial spondyloarthritis; Reuma.pt, Portuguese Register for Rheumatic Diseases; Reuma.pt (Portuguese Register for Rheumatic Diseases); SCQM, (Swiss Clinical Quality Management cohort); SPACE, (SPondyloArthritis Caught Early cohort); UCSF, (University of California San Francisco axSpA cohort)).

DISCUSSION

'"Classification criteria are standardised definitions that are primarily intended to create well-defined, relatively homogeneous cohorts of patients for clinical research; they are not intended to capture every single patient but rather to capture the majority of patients who share key features of the condition"'.[12] Patients with axSpA with radiographic sacroiliitis are traditionally classified according to the mNY criteria and more recently according to the ASAS criteria. The data presented in this study show that patients with axSpA classified as AS according to mNY criteria and those classified as r-axSpA according to ASAS criteria are mostly the same. Nonetheless, there is minor disagreement, mainly due to age at onset of back pain. The latter is reported by patients at the time of diagnosis in almost all cohorts and therefore susceptible to recall bias, a valid concern especially for the cohorts

containing patients with a long disease duration and long gap between symptom onset and diagnosis. The age criterion was introduced with the implementation of the ASAS criteria in 2009; this was mainly based on data from Feldtkeller *et al,*.[13] which showed that 95% of AS patients reported an age of onset <45 years. Based on this fact, one would expect around 5% of the patients fulfilling the mNY criteria not to fulfil the ASAS criteria. In this study, this percentage is 7%.

Due to the nature of the data and the slight differences between the two criteria sets some assumptions had to be made, which is a limitation to this study. The first assumption concerns IBP; in general, the ASAS definition of IBP[10] was used. However, if this was unavailable (and could not be defined from individual components of IBP), the rheumatologist's assessment as provided in the dataset was used instead. The second assumption regards mobility limitations; according to the mNY criteria, mobility limitations are to be identified based on age-adjusted and gender-adjusted comparisons; however, in the original publication no reference values were provided. Therefore, reference values resulting from the MOBILITY study[11] were used. If information on mobility was unavailable, the rheumatologist's judgement of 'restricted mobility' as provided in the dataset was used. Both assumptions may have influenced the proportion of patients fulfilling either of the criteria sets.

As shown in the HLA-B27 analysis, the mNY+/ASAS- group showed a lower percentage of HLA-B27 positives. HLA-B27 positivity is associated with earlier disease onset,[13–15] which may explain the low percentage of HLA-B27+ inthe mNY+/ASAS- group (48%) and is in line with the highest HLA-B27 positivity (72%) in the mNY-/ASAS+ group. An alternative explanation may be that patients in the mNY+/ASAS- group are misclassified as having r-axSpA as a higher HLA-B27 percentage is expected in mNY+ patients. The overall percentage of HLA-B27 found in this study is relatively low, which may be due to the local readings of the radiographs that may have resulted in false classifications for both classification sets.[16]

In conclusion, this study found that agreement between the mNY and ASAS r-axSpA criteria is very high, which supports the interchangeable use of the terms AS and r-axSpA. This has important implications for the axSpA research field, since older literature used mNY and AS, whereas more recent literature often uses ASAS criteria and r-axSpA. Acknowledging that both criteria sets identify the same patients implies that older literature on AS and newer literature on r-axSpA can be directly compared.

SUPPLEMENTARY DATA

Supplementary data are published online on the website of the Annals of Rheumatic Diseases

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