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ORIGINAL RESEARCH

Impact of patient characteristics on ASDAS disease activity state cut-offs in axial spondyloarthritis: results from nine European rheumatology registries

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ABSTRACT

Objectives To re-evaluate cut-offs for disease activity states according to the Axial Spondyloarthritis Disease Activity Score (ASDAS), and study the impact of sex, age, calendar time, disease and symptom duration on ASDAS and ASDAS cut-offs in a large contemporary cohort.

Methods Data from 2939 patients with axial spondyloarthritis (axSpA) starting their first tumour necrosis factor inhibitor in nine European registries were pooled and analysed. Receiver operating characteristic analyses were performed to identify cut-offs against external criteria. Six-month data including patient and physician global assessments, both ≤1 (0–10 integer scale), and Assessment of SpondyloArthritis International Society partial remission were used for separation of inactive disease (ID) from low disease activity (LDA), while patient and physician global ≤3 were applied as external criteria to separate LDA from high disease activity (HDA). Patient and physician global ≥6 were applied to separate HDA from very high disease activity in baseline data.

Results The three ASDAS cut-offs identified to separate the four disease activity states in the overall patient population were <1.3, <2.0 and >3.5. Cut-offs for ID and LDA in women were higher (<1.5 and <2.0, respectively) than in men (<1.3 and <1.9), as were cut-offs in patients ≥45 years (<1.5 and <2.2) versus ≤34 years (<1.2 and <1.9) and 35–44 years (<1.3 and <1.8). Cut-offs were independent of calendar time and disease duration.

Conclusions Re-evaluation of ASDAS cut-offs for disease activity states in a large multi-national axSpA cohort resulted in cut-offs similar to those currently endorsed. Differences in cut-offs between sex and age groups for ID and LDA were observed, but the differences were minor.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Axial Spondyloarthritis Disease Activity Score with C reactive protein (ASDAS) is a validated composite outcome measure for assessment of disease activity in axial spondylarthritis.

⇒ Cut-offs for disease activity states are crucial for implementation of treat-to-target strategies and were developed for ASDAS in a smaller single-centre cohort in 2011.

WHAT THIS STUDY ADDS

⇒ Re-evaluating the cut-offs for ASDAS disease activity states in a large multi-national cohort confirmed the validity of the current OMERACT endorsed cut-offs.

⇒ The selected cut-offs differed between sexes and age-groups, while similar cut-offs were selected across disease duration and calendar year of treatment initiation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Understanding potential differences in cut-offs for disease activity states between certain patient groups might facilitate the implementation of individualised treatment goals.

INTRODUCTION

Over the past decade, the benefit of a treatment strategy aiming to achieve a predefined treatment target has been demonstrated for patients with inflammatory arthritis.[1 2] To implement such a strategy, valid outcome measures and cut-offs for relevant disease activity state targets, that is, low disease activity (LDA) or remission, are needed.

In axial spondyloarthritis (axSpA), the Assessment of SpondyloArthritis International Society (ASAS) group has developed the Axial Spondyloarthritis Disease Activity Score with C reactive protein (ASDAS), a composite outcome measure with continuous measurement properties, fulfilling important aspects of truth, feasibility and discrimination.[3] ASAS also developed cut-off values for ASDAS disease activity states, that is, inactive disease (ID), LDA, high disease activity (HDA) and very high disease activity (VHDA), according to several external criteria.[4] The cut-offs were developed in a cohort of 477 patients with ankylosing spondylitis (AS) from the Norwegian Disease-Modifying Anti-Rheumatic Drug study (five-centre register NOR-DMARD), who initiated a new conventional or biological DMARD between the years of 2000 and 2010.[4] Cross-validation was performed in 223 patients from the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy trial of AS, and the disease activity states and their respective cut-off values were endorsed by OMERACT[5] and have subsequently been applied as endpoints in a large number of randomized controlled trials (RCTs) and observational studies.[6–9] The only treat-to-target (T2T) study conducted in axSpA patients to date also applied these ASDAS disease activity states, targeting LDA. Of note, in the Tight Control in Spondyloarthritis study, the primary endpoint, which was the proportion of patients with ≥30% improvement in the ASAS-Health Index, was not improved by a T2T strategy compared with usual care.[10]

While a uniform and agreed definition of disease activity states for the 'global' patient population is indeed valuable, it has become evident that the case mix of development cohorts impacts the derived cut-off values for disease activity states, a phenomenon also known from the Minimal Clinical Important Difference.[11 12] In a cohort of AS patients from Taiwan, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) cut-off value corresponding to ASDAS HDA was 3.9,[13] while the same value was found to be 4.9 in 333 axSpA patients in Korea.[14] Specific patient characteristics also seem to impact cut-offs for different outcome measures, as cut-offs for BASDAI disease activity states differed according to symptom duration in the Taiwanese cohort, while cut-offs for ASDAS disease activity states were generally higher when derived in women compared with men in a Turkish single centre study.[13 15] The impact of such differences is currently not well understood but could potentially impact the success and validity of T2T strategies.

The European Spondyloarthritis (EuroSpA) Research Collaboration Network (RCN) was established to allow secondary use of real-world data from large numbers of patients included in 16 existing quality registries and observational cohorts.[7] Based on data from the EuroSpA RCN, we aimed to investigate two main hypotheses, (1) the overall ASDAS cut-offs for disease activity states would differ from the endorsed cut-offs if developed in a larger, heterogenous and more recent cohort of European axSpA patients, and (2) sex, age, calendar year of treatment initiation, disease duration and symptom duration would impact the ASDAS and cut-offs for disease activity states.

METHODS

Patients and assessments

This study used data from nine European routine care registries participating in the EuroSpA Research Collaboration Network; ATTRA (Czech Republic), Biorx.si (Slovenia), DANBIO (Denmark), ICEBIO (Iceland), Reuma.pt (Portugal), ROB-FIN (Finland), SCQM (Switzerland), SRQ (Sweden) and TURKBIO (Turkey). Bionaïve adult patients with a clinical diagnosis of axSpA (radiographic or non-radiographic), who initiated a first tumour necrosis factor inhibitor (TNFi) between 1 January 2009 and 31 December 2018, were included if they had available data on the individual components of ASDAS and the relevant external criteria (patient and physician global assessments, BASDAI and Bath Ankylosing Spondylitis Functional Index (BASFI)) at a baseline visit (−30 to +30 days from treatment start) and a follow-up visit at 6 months (90–270 days from treatment start) during TNFi treatment.

The registration of patient-reported outcomes (PROs) varied across registries and PROs, with BASDAI components, BASFI, physician global and patient global assessments registered on 0–100 mm Visual Analogue Scales (VAS) and 0–10 Numeric Rating Scales (NRS) scales. For this study, PROs in 0–100 VAS were converted to 0–10 NRS by rounding to the nearest integer.

Cohorts

Patients were stratified according to preselected baseline characteristics that were expected to be of potential relevance based on clinical experience: (a) sex, (b) age (≤34 years, 35–44 years and ≥45 years), (c) calendar period of treatment start (between 2009 and 2014 vs 2015 and 2018), (d) disease duration (≤1 year, 2–5 years and ≥6 years) and (e) symptom duration (≤2 years vs ≥3 years). To explore the combined impact of sex and age, the cohorts consisting of men and women were further stratified according to age as in (b). As a sensitivity analysis, cohorts stratified according to sex were additionally stratified by registry.

Statistical methods

Overall, we followed the methodology originally applied by Machado *et al* to select ASDAS cut-offs.[4] Thus, follow-up data (6 months) were used to select the cut-offs for ID and between LDA and HDA, while baseline data were used to select the cut-off for VHDA in order to ensure the best representation of the disease activity state studied.

Receiver operating characteristics (ROC) analyses against external criteria were used to determine cut-off values. To encompass both patient and physician perspectives, predefined values of patient and physician global assessments (both ≤1) and ASAS partial remission were

used as external criteria for separation of ID from LDA. To separate LDA from HDA, patient global ≤3 and physician global ≤3 were applied as external criteria, while patient global ≥6 and physician global ≥6 were applied to separate HDA from VHDA.

To explore the relationship between BASDAI and ASDAS, BASDAI cut-offs of <1, <1.5 and <2, respectively, were compared with the cut-off between ID and LDA, while BASDAI cut-offs of <3, <3.5 and <4, respectively, were compared with the cut-off between LDA and HDA. Finally, BASDAI cut-offs of >5, >5.5 and >6, respectively, were compared with the cut-off between HDA and VHDA.

Since PROs in 0–100 VAS were converted to 0–10 NRS by rounding to the nearest integer, the selected cut-offs for the external criteria patient global and physician global assessments were adapted compared with Machado *et al*,[4] as values strictly less than 1 (<1) on a 0–10 NRS, corresponded to values equal to or less than 1 (≤1) in our converted data. The BASDAI cut-offs were unaffected due to the continuous nature of the composite BASDAI score.

In alignment with Machado *et al*, three methods of 'optimal' cut-off determination were applied, (1) fixed 90% specificity, (2) the Youden index and (3) the point closest to (0.1), that is the point where the shoulder of the ROC curve is closest to the left upper corner of the graphic. When choosing the final presented cut-off, the 90% specificity criterion was prioritised for ID and LDA, as this criterion minimises the risk of wrongly classifying patients as being in ID or LDA, which is a clinical situation that should be avoided. For VHDA, the Youden index and the closest point to (0, 1) was prioritised to obtain the best balance between sensitivity and specificity.[16] The level of agreement between disease activity states based on the overall and the age- and sex-stratified cut-offs was assessed using proportion of discordance.

RESULTS

Patient characteristics

From 16 414 axSpA patients who initiated a first TNFi between 1 January 2009 and 31 December 2018, 2939 patients were included in the analyses (overall cohort), while 13 475 were excluded due to missing assessment of either ASDAS, BASDAI, BASFI or physician global at baseline or at the 6-month follow-up visit. Patients included in the overall cohort were predominantly men (61%) with a median age of 40 years at TNFi start. The majority of patients were Human Leucocyte Antigen B27 positive (80%), and baseline disease activity was high with a median ASDAS of 3.7 and a median BASDAI of 5.8 (table 1).

Compared with the overall cohort, patients excluded from the analyses had lower levels of inflammatory markers (median C reactive protein (CRP) 8 mg/L vs 12 mg/L, erythrocyte sedimentation rate (ESR) 16 mm/hour vs 25 mm/hour), but similar demographic characteristics and PROs at baseline (table 1). Similarly, the overall cohort of excluded patients had lower CRP at 6 months compared with the included patients, while PROs were comparable (table 2 and online supplemental table S1). Differences across stratifications in the excluded patients were consistent with findings in the included patients.

For patient characteristics and baseline disease activity in the stratified cohorts, see online supplemental tables S2–S6.

Disease activity across stratifications

Disease activity at baseline and after 6 months of TNFi treatment, as measured by the individual components of ASDAS and the composite ASDAS, are presented in table 2 for the overall cohort and the cohorts stratified by sex, age, calendar year of treatment start and disease and symptom duration. At baseline, the PROs were very similar across all stratifications with mean values of BASDAI question 2 (spinal pain), ranging from 6.6 to 6.9 in all cohorts. Mean CRP levels were higher in men (22.1 mg/L) than in women (15.1 mg/L), but were similar across stratifications by calendar time, age, disease and symptom duration. At 6 months, mean (SD) ASDAS was, as expected, markedly lower across all stratifications. Notably, 6-month ASDAS was lower in men (1.9) than in women (2.2) and in patients ≤34 years (1.8) and between 35 and 44 years (1.9) compared with patients ≥45 years (2.3). Across these age groups CRP levels were comparable, while PROs differed.

In online supplemental table 7 disease activity measures and treatment outcomes other than the components of ASDAS are presented. In line with the findings above, differences in both PROs, physician global and treatment retention were observed between men and women, and between age groups, while outcomes were comparable across stratifications by calendar time, disease- and symptom duration.

ASDAS-CRP cut-offs for disease activity states in the overall cohort

In table 3, cut-offs for disease activity states based on the selected external criteria according to the three methods for cut-off determination in the overall cohort are presented.

Overall, we observed consistent results between patient global scores, physician global scores and ASAS partial remission as external criteria, and the final cut-offs selected in the overall cohort were ASDAS <1.3, <2.0 and >3.6.

The BASDAI cut-off of <1 corresponded best to the cut-off between ID and LDA (<1.3), while BASDAI cut-off of <3 corresponded to the cut-off between LDA and HDA (<2.0). For the cut-off between HDA and VHDA (>3.6), BASDAI cut-offs of >5, >5.5 and >6 corresponded equally well (table 3).

ASDAS cut-offs for disease activity states in stratified cohorts

In table 4, the final cut-offs for disease activity states selected in the stratified cohorts are shown. The selected

Table 1 Patient characteristics and disease activity at baseline in patients included in the analyses compared with those who could not be included

	Included patients—overall cohort* (n=2939)		Patients not included* (n=13 475)	
	Available data n (%)	Value	Available data n (%)	Value
Age, years	2939 (100%)	40 (32–49)	13 475 (100%)	41 (32–51)
Age at diagnosis, years	2812 (96%)	34 (27–43)	10 550 (78%)	34 (27–44)
Disease duration, years	2812 (96%)	3 (1–8)	10 550 (78%)	2 (0–7)
Disease duration, years, mean (SD)	2812 (96%)	5.4 (7.1)	10 550 (78%)	5.4 (8.1)
Symptom duration, years	2536 (86%)	9 (4–16)	11 110 (82%)	8 (3–17)
Symptom duration, years, mean (SD)	2536 (86%)	11.0 (9.2)	2536 (86%)	11.4 (10.9)
Men, n (%)	2939 (100%)	1783 (61%)	13 475 (100%)	7752 (58%)
BMI, kg/m^2	1896 (65%)	26.0 (23.3–29.4)	4573 (34%)	25.6 (23.0–29.0)
Current smokers, n (%)	2766 (94%)	881 (32%)	11 220 (83%)	2592 (23%)
HLA-B27 positive, n (%)	1856 (63%)	1492 (80%)	4387 (33%)	3216 (73%)
Fulfilling the Modified New York criteria, n (%)	695 (24%)	475 (68%)	2535 (19%)	1729 (68%)
Fulfilling the ASAS criteria, n (%)	1743 (59%)	1721 (99%)	3781 (28%)	3681 (97%)
TNF inhibitor, n (%)	2939 (100%)		13 475 (100%)	
Infliximab		646 (22%)		3349 (25%)
Etanercept		543 (19%)		3329 (25%)
Adalimumab		931 (32%)		4089 (30%)
Certolizumab pegol		198 (7%)		615 (5%)
Golimumab		617 (21%)		2097 (16%)
Calendar year of treatment start, n (%)	2939 (100%)		13 475 (100%)	
2009–2014		988 (34%)		7896 (59%)
2015–2018		1947 (66%)		5583 (41%)
CRP, mg/L	2939 (100%)	12 (5–25)	8731 (65%)	8 (3–19)
ESR, mm/hour	1726 (59%)	25 (12–39)	6411 (48%)	16 (7–32)
Patient pain (0–10)	2628 (89%)	7 (5–8)	7241 (54%)	7 (5–8)
Patient fatigue (0–10)	1325 (45%)	7 (5–8)	4224 (31%)	7 (5–8)
Patient global (0–10)	2939 (100%)	7 (5–8)	7274 (54%)	7 (5–8)
Physician global (0–10)	2939 (100%)	5 (2–7)	3439 (26%)	4 (2–6)
HAQ (0–3)	2219 (76%)	0.9 (0.6–1.4)	5553 (41%)	0.8 (0.5–1.2)
BASDAI (0–10)	2939 (100%)	5.8 (4.4–7.2)	6235 (46%)	6.0 (4.5–7.3)
BASDAI Question 1—fatigue (0–10)	2939 (100%)	6 (5–8)	6308 (47%)	7 (5–8)
BASDAI Question 2—spinal pain (0–10)	2939 (100%)	7 (6–8)	6393 (47%)	7 (5–8)
BASDAI Question 3—joint pain (0–10)	2939 (100%)	5 (2–6)	6334 (47%)	5 (2–7)
BASDAI Question 4—tenderness (0–10)	2939 (100%)	5 (3–7)	6319 (47%)	6 (3–8)
BASDAI Question 5—severity morning stiffness (0–10)	2939 (100%)	7 (4–8)	6674 (50%)	7 (5–8)
BASDAI Question 6—duration morning stiffness (0–10)	2939 (100%)	5 (3–8)	6733 (50%)	5 (3–8)
BASFI (0–10)	2877 (98%)	4.6 (2.6–6.6)	5934 (44%)	4.5 (2.5–6.5)
ASDAS	2939 (100%)	3.7 (3.1–4.3)	4363 (32%)	3.4 (2.8–4.0)
ASDAS-ESR	1726 (59%)	3.6 (3.0–4.2)	2923 (22%)	3.1 (2.5–3.8)

Values are median (25% percentile to 75% percentile) unless otherwise stated.
Available data n (%): number and percentage of patients with registered data for the specific variable.
*Patients could be included if they had available assessment of ASDAS, BASDAI, BASFI and physician global at baseline and at 6-month follow-up.
ASDAS, Axial Spondyloarthritis Disease Activity Score based on CRP; ASDAS-ESR, Axial Spondyloarthritis Disease Activity Score based on ESR; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HLA-B27, Human Leucocyte Antigen B27; TNF inhibitor, tumor necrosis factor inhibitor.

Table 2 Baseline and 6 months' values of ASDAS and components in cohorts stratified by sex, calendar time, age, disease and symptom duration

	Overall	Sex		Calendar time		Age			Disease duration			Symptom duration	
		Men	Women	2009–2014	2015–2018	≤34 years	35–44 years	≥45 years	≤1 year	2–5 years	≥6 years	≤2 years	≥3 years
	n=2939	n=1785	n=1154	n=989	n=1950	n=912	n=972	n=1055	n=1149	n=714	n=949	n=410	n=2126
Baseline disease activity													
BASDAI question 2—spinal pain	6.8 (2.2)	6.7 (2.2)	6.9 (2.2)	6.9 (2.1)	6.7 (2.2)	6.6 (2.3)	6.8 (2.1)	6.9 (2.1)	6.7 (2.2)	6.6 (2.2)	6.9 (2.1)	6.3 (2.5)	6.8 (2.1)
BASDAI question 3—joint pain	4.9 (2.9)	4.7 (2.9)	5.2 (2.9)	5.1 (3.0)	4.8 (2.9)	4.4 (3.0)	4.8 (2.9)	5.4 (2.9)	4.9 (3.0)	4.7 (2.9)	5.1 (2.9)	5.0 (2.9)	4.8 (2.9)
BASDAI question 6—duration morning stiffness	5.5 (2.9)	5.6 (2.9)	5.4 (2.9)	5.9 (2.9)	5.3 (2.9)	5.4 (2.9)	5.5 (3.0)	5.6 (2.9)	5.5 (2.9)	5.3 (2.9)	5.7 (2.9)	5.0 (3.0)	5.6 (2.9)
Patient global	6.5 (2.2)	6.4 (2.2)	6.6 (2.2)	6.6 (2.2)	6.5 (2.2)	6.4 (2.3)	6.5 (2.1)	6.6 (2.1)	6.7 (2.2)	6.3 (2.2)	6.5 (2.1)	6.6 (2.3)	6.5 (2.2)
CRP, mg/L	19.3 (23.6)	22.1 (24.9)	15.1 (20.6)	20.1 (23.5)	19.0 (23.6)	20.2 (23.9)	18.2 (20.5)	19.7 (25.8)	19.1 (26.5)	18.6 (22.1)	20.6 (20.9)	19.8 (27.1)	19.6 (22.1)
ASDAS	3.7 (0.9)	3.7 (0.9)	3.6 (0.9)	3.8 (0.9)	3.6 (0.9)	3.6 (1.0)	3.7 (0.9)	3.7 (0.9)	3.6 (0.9)	3.6 (1.0)	3.8 (0.9)	3.6 (1.0)	3.7 (0.9)
6-month disease activity													
BASDAI question 2—spinal pain	3.3 (2.7)	3.0 (2.5)	3.8 (2.9)	3.5 (2.7)	3.2 (2.7)	2.7 (2.6)	3.1 (2.6)	4.0 (2.8)	3.5 (2.9)	3.1 (2.6)	3.1 (2.5)	3.2 (2.8)	3.2 (2.7)
BASDAI question 3—joint pain	2.3 (2.6)	2.0 (2.4)	2.8 (2.8)	2.4 (2.6)	2.3 (2.6)	1.7 (2.3)	2.1 (2.4)	3.1 (2.8)	2.5 (2.8)	2.1 (2.5)	2.1 (2.4)	2.3 (2.7)	2.2 (2.5)
BASDAI question 6—duration morning stiffness	2.5 (2.6)	2.3 (2.5)	2.7 (2.7)	2.7 (2.7)	2.3 (2.6)	2.0 (2.4)	2.3 (2.5)	3.0 (2.8)	2.6 (2.7)	2.2 (2.5)	2.4 (2.4)	2.4 (2.6)	2.3 (2.5)
Patient global	3.2 (2.6)	2.9 (2.4)	3.7 (2.7)	3.3 (2.5)	3.2 (2.6)	2.7 (2.5)	3.1 (2.5)	3.9 (2.6)	3.5 (2.8)	3.0 (2.5)	3.0 (2.4)	3.3 (2.6)	3.1 (2.5)
CRP, mg/L	6.0 (11.4)	6.1 (12.7)	5.8 (9.1)	5.8 (11.5)	6.1 (11.3)	5.5 (10.1)	5.3 (8.6)	7.0 (14.3)	5.9 (11.4)	5.9 (11.3)	6.1 (11.1)	6.6 (13.5)	5.9 (10.4)
ASDAS	2.0 (1.0)	1.9 (1.0)	2.2 (1.0)	2.1 (1.0)	2.0 (1.0)	1.8 (1.0)	1.9 (0.9)	2.3 (1.0)	2.1 (1.0)	1.9 (1.0)	1.9 (0.9)	2.0 (1.0)	2.0 (1.0)

Values are mean (SD).
ASDAS, Axial Spondyloarthritis Disease Activity Score based on CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein.

Table 3 ROC analysis: ASDAS cut-offs for disease activity states according to several external criteria and according to three different methods of 'optimal' cut-off determination

ASDAS cut-offs and external criteria	n (P+N)	90% SP (SE/SP)	Youden (SE/SP)	(0, 1) (SE/SP)	AUC
Cut-offs between inactive disease and low disease activity					
ASAS partial remission	2939 (652+2287)	**<1.23** (0.82/0.90)	<1.22 (0.82/0.91)	<1.30 (0.85/0.87)	0.95
Patient global≤1	2939 (916+2023)	**<1.33** (0.77/0.90)	<1.48 (0.84/0.85)	<1.48 (0.84/0.85)	0.93
Physician global≤1	2939 (1784+1155)	<**1.40** (0.49/0.90)	<1.63 (0.60/0.84)	<1.90 (0.69/0.74)	0.78
BASDAI<1	2939 (755+2184)	<1.23 (0.71/0.90)	<1.51 (0.86/0.79)	<1.39 (0.81/0.83)	0.91
BASDAI<1.5	2939 (1080+1859)	<1.44 (0.78/0.90)	<1.52 (0.82/0.88)	<1.52 (0.82/0.87)	0.92
BASDAI<2	2939 (1342+1597)	<1.61 (0.80/0.90)	<1.63 (0.80/0.89)	<1.74 (0.85/0.85)	0.93
Cut-offs between low disease activity and high disease activity					
Patient global≤3	2939 (1817+1122)	**<1.96** (0.82/0.90)	<1.95 (0.82/0.91)	<2.00 (0.83/0.89)	0.94
Physician global≤3	2939 (2583+356)	**<1.97** (0.61/0.90)	<2.18 (0.68/0.87)	<2.37 (0.75/0.79)	0.84
BASDAI<3	2939 (1753+1186)	<1.95 (0.84/0.90)	<1.94 (0.83/0.90)	<1.98 (0.85/0.89)	0.94
BASDAI<3.5	2939 (1945+994)	<2.11 (0.84/0.90)	<2.02 (0.81/0.94)	<2.09 (0.84/0.91)	0.94
BASDAI<4	2939 (2108+831)	<2.22 (0.84/0.90)	<2.09 (0.80/0.96)	<2.27 (0.86/0.88)	0.95
Cut-offs between high disease activity and very high disease activity					
Patient global≥6	2939 (2081+858)	>4.01 (0.47/0.90)	**>3.47** (0.73/0.72)	**>3.47** (0.73/0.72)	0.81
Physician global≥6	2939 (1186+1753)	>4.59 (0.27/0.90)	**>3.72** (0.68/0.64)	**>3.72** (0.68/0.64)	0.71
BASDAI>5	2939 (1882+1057)	>4.01 (0.51/0.90)	>3.63 (0.69/0.78)	>3.61 (0.71/0.76)	0.82
BASDAI>5.5	2939 (1646+1293)	>4.08 (0.52/0.90)	>3.63 (0.74/0.76)	>3.63 (0.74/0.76)	0.83
BASDAI>6	2939 (1353+1586)	>4.20 (0.51/0.90)	>3.65 (0.79/0.70)	>3.70 (0.75/0.74)	0.83

ASAS partial remission criteria are fulfilled if the value of the following four domains is below 2 (0–10 scale): spinal pain, physical function measured by the BASFI, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness). The selected cut-offs are highlighted in bold. Range of BASDAI and patient and physician global assessment is 0–10 (0, 1), cut-off according to the closest point to (0, 1) criterion; 90% SP, cut-off according to the 90% specificity criterion.
ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Axial Spondyloarthritis Disease Activity Score based on C reactive protein; AUC, area under the curve; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; P+N, number of positive+negative results according to the external criterion; ROC, receiver operating characteristic; SE, sensitivity; SP, specificity; Youden, cut-off according to the Youden Index Criterion.

cut-offs between ASDAS ID and LDA ranged from <1.2 to <1.5, between LDA and HDA from <1.8 to <2.2 and between HDA and VHDA from >3.5 to >3.7. When cohorts were stratified based on calendar year of treatment start, disease and symptom duration, consistent cut-offs were selected, while stratification based on sex and age led to variation in the selected cut-offs, most markedly in the age-stratified cohorts (table 4).

When the cohort stratified by sex was additionally stratified by registry, the cut-off between ID and LDA was lower for men than for women in all registries, while the cut-off between LDA and HDA showed an inconsistent pattern (online supplemental table 8).

Age- and sex-stratified cut-offs for ASDAS disease activity states

When cut-offs for disease activity states were determined in cohorts stratified by both age and sex, the lowest cut-off between ID and LDA was <1.2, which was identified in men who were less than 34 years, while the highest was <1.5 selected in women who were 45 years or older. Similarly, the lowest cut-off between LDA and HDA (<1.8) was found in the youngest male cohort, while cut-offs of <2.2, <2.0 and <2.1 were identified in the female age groups and the oldest male cohort (table 5).

Comparing the age- and sex-stratified cut-offs with the overall cut-offs demonstrated that at baseline 4.3% of patients changed disease activity state, while 10.1% changed disease activity state at 6-month follow-up. The proportion of patients who changed disease activity state was highest at 6 months in men between 35 and 44 years (13.5%) (table 6).

DISCUSSION

In this study, we set out to re-evaluate the cut-offs for disease activity states in axSpA as assessed by ASDAS in a large multi-national cohort, and to explore the extent to which the cut-offs for disease activity states differed when they were selected in cohorts of axSpA patients stratified by certain patient characteristics. Overall, we identified cut-offs that largely matched the currently endorsed cut-off values, although we did demonstrate an impact of sex and age on cut-off values, while cut-offs were comparable

Table 4 ASDAS cut-offs for disease activity states selected in the entire patient population and in cohorts stratified by sex, age, calendar time, disease and symptom duration duration

Stratifications	Number of patients	Cut-off between ID and LDA	Cut-off between LDA and HDA	Cut-off between HDA and VHDA
Reference (Machado *et al*[4])		<1.3	<2.1	>3.5
Overall	2939	<1.3	<2.0	>3.6
Sex				
Male	1785	<1.3	<1.9	>3.6
Female	1154	<1.5	<2.0	>3.5
Age				
≤34 years	912	<1.2	<1.9	>3.6
35–44 years	972	<1.3	<1.8	>3.6
≥45 years	1055	<1.5	<2.2	>3.6
Calendar time				
2009–2014	989	<1.4	<2.0	>3.7
2015–2018	1950	<1.3	<2.0	>3.6
Disease duration				
≤1 year	1149	<1.3	<2.0	>3.6
2–5 years	714	<1.3	<1.9	>3.6
≥6 years	949	<1.3	<2.0	>3.6
Symptom duration				
≤2 years	410	<1.3	<1.9	>3.5
≥3 years	2126	<1.3	<1.9	>3.6

Green: selected cut-off identical to endorsed cut-off; blue: selected cut-off lower than endorsed cut-off; yellow: selected cut-off higher than endorsed cut-off.
ASDAS, Axial Spondyloarthritis Disease Activity Score based on C reactive protein; HDA, high disease activity; ID, inactive disease; LDA, low disease activity; VHDA, very high disease activity.

across different calendar years and disease and symptom durations.

Prior to stratification, cut-offs were identified in the overall study cohort of approximately 3,000 axSpA patients treated in clinical practice across Europe and monitored in registries participating in the EuroSpA collaboration.[7 17] Our methodological approach was identical to the methods applied to identify the endorsed cut-offs,[5] and the identified overall cut-offs in our study were very similar (<1.3, <2.0 and >3.5) to the endorsed cut-offs (<1.3, <2.1 and >3.5). In previous smaller studies from Turkey, which also applied the ROC-based method, comparable cut-offs between LDA and HDA and between HDA and VHDA were found, while higher cut-offs between ID and LDA (<1.6 and <1.7) were observed.[15 18] The fact that we identified cut-offs similar to those originally endorsed in a larger, heterogeneous and more recent cohort than the original development cohort is reassuring and provides further validation of the endorsed cut-offs.

Different cut-offs for disease activity states in men and women, as seen in this study, have also been reported in a smaller Turkish study, that identified a higher cut-off between ID and LDA in women (≈1.7) than in men (≈1.6).[15] As in our study, female patients had higher baseline scores for PROs, including the PROs that are part of ASDA, while CRP and ESR levels were higher in men. Numerous studies have shown sex differences in treatment outcomes in axSpA[19–22] and based on our findings it could be hypothesised that such a difference would decrease if sex-specific cut-offs were applied. However, in our cohort only 10% of patients changed disease activity states when the age- and sex-stratified cut-offs were applied, why testing the defined sex-specific cut-offs in an external cohort would be a necessary next step to understand whether the observed differences in cut-offs values are actually clinically relevant.

While younger age at treatment initiation is a known predictor of a more favourable treatment response,[23 24] there are no prior studies exploring the impact of age on cut-offs for disease activity states. We found lower cut-off values for ID in the younger cohorts compared with the cohort aged 45 years and older. Similarly, lower cut-offs for LDA were found in the younger cohorts suggesting a definite impact of age. This was most pronounced in men, but also present in women. Due to the large number of patients in our overall cohort, the six age- and sex-stratified cohorts included at least 300 patients each, despite the different age distributions in men and women, with a later median age at disease onset in the

Table 5 ASDAS cut-offs for disease activity states determined in cohorts stratified by sex and age

	Age		
	≤34 years	35–44 years	≥45 years
Cut-off between ID and LDA			
Sex			
Male	<1.2 (n=584)	<1.2 (n=614)	<1.4 (n=587)
Female	<1.3 (n=328)	<1.5 (n=358)	<1.5 (n=468)
Cut-off between LDA and HDA			
Sex			
Male	<1.8 (n=584)	<1.8 (n=614)	<2.1 (n=587)
Female	<2.2 (n=328)	<2.0 (n=358)	<2.1 (n=468)
Cut-off between HDA and VHDA			
Sex			
Male	>3.7 (n=584)	>3.6 (n=614)	>3.6 (n=587)
Female	>3.4 (n=328)	>3.5 (n=358)	>3.6 (n=468)

Green: selected cut-off identical to endorsed cut-off; blue: selected cut-off lower than endorsed cut-off; yellow: selected cut-off higher than endorsed cut-off.
ASDAS, Axial Spondyloarthritis Disease Activity Score based on C reactive protein; HDA, high disease activity; ID, inactive disease; LDA, low disease activity; VHDA, very high disease activity.

female (37 years) than the male (33 years) cohorts. Such a difference in age distributions has also been reported previously.[25] In contrast, stratification on disease and symptom duration and calendar year of treatment initiation had no impact on the cut-offs. This again points to age and sex as the main demographic factors impacting cut-off selection.

While ASDAS is the currently preferred disease activity measure in axSpA, the BASDAI is still widely used and in some clinical settings (ie, when no CRP is available) it is used as the only available disease activity measure.[2] To better understand the relationship between ASDAS and BASDAI, we compared the cut-offs for disease activity states according to various BASDAI values as external criteria in the overall cohort. Importantly, we found that BASDAI cut-offs of 1 and 3 were those that were most comparable to the ASDAS cut-offs for ID and LDA, which is lower than the widely used cut-off of 4 for LDA and the proposed cut-off of 2 for BASDAI remission.[14]

Table 6 Discordance of Axial Spondyloarthritis Disease Activity Score disease activity states between overall and age- and sex-stratified cut-offs

	Baseline	6 months
Overall	127/2939 (4.3%)	298/2939 (10.1%)
Male ≤34 years	50/584 (8.6%)	67/584 (11.5%)
Male 35–44 years	8/614 (1.3%)	83/614 (13.5%)
Male ≥45 years	6/587 (1.0%)	48/587 (8.2%)
Female ≤34 years	36/328 (11.0%)	25/328 (7.6%)
Female 35–44 years	18/358 (5.0%)	28/358 (7.8%)
Female ≥45 years	9/468 (1.9%)	47/468 (10.0%)

Our study has several limitations, mainly due to the inherent challenge of missing data in registry-based observational research. Only 15% of all patients in EuroSpA could be included in the analyses due to missing registration of either ASDAS or one of the external criteria at either of the relevant time points. However, the patient characteristics and disease activity were largely similar between included and excluded patients at both baseline and follow-up and we, therefore, believe our study cohort to be representative of the larger EuroSpA cohort. The larger EuroSpA cohort is also affected by the limitation of missing data, as data such as MRI findings and classification criteria (ASAS and/or modified New York criteria) are registered only in a minority of the quality registries that participate in the EuroSpA RCN. The heterogeneity in registration practice across registries is also reflected in the timepoint for assessment of treatment effectiveness, that is, the 6-month follow-up visit that could have taken place between 90 and 270 days after treatment initiation. The wide interval was chosen to maximise data availability, while respecting the guidelines from ASAS-EULAR stating that treatment effect should be assessed after at least 12 weeks.[2 26]

It would also have been relevant to explore the impact of patient characteristics on improvement scores, but the necessary external anchor for change in health status over time was not sufficiently recorded in the registries. Likewise, information on Patient Acceptable Symptom State and comorbid fibromyalgia was not available for analyses. In addition, due to limited registration of radiographic status, we were unable to stratify patients into radiographic and non-radiographic axSpA. Previously, Kilic *et al* analysed radiographic and non-radiographic axSpA patients separately and found similar cut-offs,[18] which is why we consider this to be a minor limitation.

In conclusion, we used a large multi-national data set of axSpA patients treated in routine clinical practice to re-evaluate the cut-offs for disease activity states according to ASDAS and investigated whether certain patient characteristics impact the cut-offs for disease activity states. Our findings validate the current cut-offs endorsed by OMERACT for the overall population. While our analyses demonstrated a certain impact of age and sex on cut-off values, these differences are not of a size that warrants any change of the well-known cut-offs to be applied in studies and T2T strategies, but may inform the clinical rheumatologist

when assessing the disease activity in an individual patient.

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