Factors Associated With Residual Disease in Axial Spondyloarthritis

The Journal of Rheumatology 2023;50:1430–8
doi:10.3899/jrheum.2023-0194
First Release August 15 2023

The Journal of Rheumatology

Factors Associated With Residual Disease in Axial Spondyloarthritis: Results From a Clinical Practice Registry

Casper Webers[1], Annelies Boonen[1], Harald E. Vonkeman[2], and Astrid van Tubergen[1]

ABSTRACT. ***Objective***. To explore residual disease, defined as substantial symptoms and disease burden despite a remission or low disease activity (LDA) state, in patients with axial spondyloarthritis (axSpA), and to determine which factors are associated with residual disease.

Methods. For this cross-sectional observational study, 1 timepoint per patient was used from SpA-Net, a web-based monitoring registry for SpA. Patients with an Ankylosing Spondylitis Disease Activity Score (ASDAS) < 2.1 (LDA) were included. Indicators of residual disease (outcomes) included fatigue (primary outcome), pain, physical functioning, health-related quality of life (HRQOL), and peripheral symptoms. Sex was the primary explanatory factor for residual disease. Other explanatory factors included demographics and disease-related factors. Associations between these factors and presence and extent of residual disease were explored using logistic and linear regression.

Results. In total, 267 patients in an LDA state were included. Mean age was 50.6 (SD 14.3) years and 100 (37.5%) were female. Residual disease occurred frequently (n = 114 [42.7%] had fatigue scores > 4/10; n = 34 [17.8%] had pain scores > 4/10), including in those in remission (ASDAS < 1.3). Physical HRQOL was reduced in 27% and moderate/poor in 33%. Multivariable regression analyses showed that reported fatigue was more severe and prevalent in female patients (fatigue severity [0–10]: B_{female} = 0.78, 95% CI 0.18-1.38; fatigue > 4/10: OR_{female} = 3.29, 95% CI 1.74-6.20). Other indicators of residual disease (ie, pain, peripheral symptoms, physical HRQOL) were also more severe and/or more prevalent in females.

Conclusion. Residual disease is frequent in patients with axSpA who are in an LDA state, including remission, and it is particularly prevalent in female patients. Future studies should address how to manage or prevent residual disease in axSpA.

Key Indexing Terms: axial spondyloarthritis, disease activity, registry, residual disease

Axial spondyloarthritis (axSpA) is a chronic inflammatory disorder of the lower spine and sacroiliac joints.[1] The key symptom is lower back pain, although other musculoskeletal sites are often also involved. In addition, extramusculoskeletal manifestations (EMMs; anterior uveitis, inflammatory bowel disease [IBD], and psoriasis [PsO]) can be present. The treatments for axSpA include nonsteroidal antiinflammatory drugs (NSAIDs), biologic disease-modifying antirheumatic drugs (bDMARDs), targeted synthetic DMARDs (tsDMARDs), and occasionally, if peripheral symptoms occur, conventional synthetic DMARDs (csDMARDs).[2] Due to the chronic nature of the disease and its early onset in life, the burden for patients and society is substantial.[3,4]

In the management of axSpA, disease activity is an important outcome. Disease activity reflects the symptoms of axSpA,[5] and higher disease activity is associated with greater progression of structural damage to the spine.[6] According to international recommendations, disease activity should be measured regularly, and low disease activity (LDA) or remission should be aimed for.[7] Disease activity in axSpA is assessed with the Ankylosing Spondylitis Disease Activity Score (ASDAS). Remission and LDA are defined as ASDAS scores < 1.3 and < 2.1, respectively.[8] These disease activity targets are used to guide treatment decisions.[9,10] In current practice, however, even patients who achieve these targets can still experience substantial symptoms and disease burden.[11] Examples of such residual disease are specific symptoms like pain and fatigue (ie, residual symptoms), signs of inflammation such as enthesitis, and also impairments in general

No specific funding was received from any bodies in the public, commercial, or not-for-profit sectors to carry out the work described in this article. SpA-Net was financially supported by grants from The Netherlands Organisation for Health Research and Development (ZonMw, project no. 836042001) and Dutch Arthritis Society, and was additionally sponsored by AbbVie, Biogen, Celgene, Janssen-Cilag, MSD, Novartis, Pfizer, and UCB.

[1]C. Webers, MD, PhD, A. Boonen, MD, PhD, A. van Tubergen, MD, PhD, Department of Medicine, Division of Rheumatology, Maastricht University Medical Centre, Maastricht, and Care and Public Health Research Institute, Maastricht University, Maastricht; [2]H.E. Vonkeman, MD, PhD, Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente, Enschede, and Department of Psychology, Health & Technology, University of Twente, Enschede, the Netherlands.

HEV has received consulting fees or honorarium from AbbVie, Novartis, Pfizer, UCB, Janssen, and Galapagos, all outside the submitted work. AvT has received unrestricted research grants related to SpA-Net from Novartis, Pfizer, and UCB, and received consulting fees from Galapagos, Novartis, and UCB. CW and AB declare no conflicts of interest relevant to this article.

Address correspondence to Dr. C. Webers, Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, PO Box 5800, Maastricht 6202 AZ, the Netherlands. Email: cjp.webers@maastrichtuniversity.nl.

Accepted for publication July 4, 2023.

health and functioning. These can affect patients' daily lives, and potentially contribute to the broader disease impact. Currently, there are no recommendations on how to manage residual disease.

The phenomenon of residual disease has repeatedly been shown in other rheumatic diseases, such as psoriatic arthritis and rheumatoid arthritis.[11-14] In axSpA, however, only 2 studies to our knowledge have investigated residual disease.[11,15] About half of patients who were in an LDA state still had fatigue or pain. Additionally, female and older patients were more likely to experience fatigue, although analyses were not adjusted for potential confounders and were limited to fatigue and pain.[15] Previous research has also shown that female patients with axSpA report more severe symptoms in general.[16,17] As such, sex is an interesting candidate risk factor to investigate in the context of residual disease, as this information could be used to identify those more vulnerable in daily practice.

The aim of this study was to determine to what extent a variety of different indicators of residual disease are present in patients with axSpA who are in remission or an LDA state in daily practice, and to explore which patient and disease characteristics (with a particular focus on sex) are associated with the presence and extent of residual disease.

METHODS

Study design and study population. Our cross-sectional, observational study was conducted within SpA-Net, a disease-specific integrated web-based system for Dutch patients with SpA (International Clinical Trials Registry Platform registration no. NTR6740).[18] SpA-Net was launched in 2016 and is used in 2 large hospitals.

All patients with a prevalent or incident clinical diagnosis of SpA who are under rheumatologists' care in participating centers are consecutively included in SpA-Net as part of routine care. Aside from a clinical diagnosis of SpA, there are no additional inclusion/exclusion criteria for participation in SpA-Net. Participants are prospectively monitored over time in daily practice. They complete questionnaires at home prior to their outpatient visits, during which these questionnaires are reviewed and additional data, such as physician-based outcomes, are registered. As SpA-Net is a daily practice registry, the frequency of visits is not fixed but varies between patients. Changes in disease management are left to the discretion of the treating rheumatologists.

For our present study, all patients with an axSpA diagnosis were eligible if they had data available on the ASDAS and on ≥ 1 indicator of residual disease (see Outcomes). If multiple timepoints for a patient met these criteria, the most recent complete assessment of the patient in an LDA state—or high disease activity (HDA) state if never in an LDA state—was chosen for analysis. Our goal was to explore a wide range of indicators of residual disease in current practice and under current management, which is why we chose the most recent, complete assessment.

The ethics committee of the University Hospital Maastricht/Maastricht University determined that observational studies involving SpA-Net were not subject to the Medical Research Involving Human Subjects Act as data were collected in routine care, and official approval was not required for this study (METC azM/UM 15-4-266). Written informed consent was obtained from each patient to use data for research.

Disease activity categories. Disease activity is measured with the ASDAS, which combines patient-reported outcome measures with a laboratory biomarker for inflammation (C-reactive protein [CRP]).[19] Disease activity states were defined as LDA (ASDAS < 2.1, including patients in remission [inactive disease, ASDAS < 1.3] or nonremission LDA [1.3 ≤ ASDAS < 2.1]) or HDA (ASDAS ≥ 2.1).[8] The ASDAS and ASDAS-based disease activity states have been validated and endorsed.[20,21]

Explanatory factors for residual disease. Sex was the primary explanatory factor. Additional factors included other patient characteristics (ie, age, education, employment, smoking) as well as disease-related factors (ie, symptom duration, history of EMMs, type of current therapy [NSAID, cs/b/tsDMARD]).

Patient characteristics were either collected upon inclusion (age and sex) or updated every 2 years (education and smoking) or 6 months (employment). Education was dichotomized (high vs other). Employment was collected as part of the Work Productivity and Activity Impairment questionnaire (employed vs not employed).[22] Former smokers and never smokers were grouped and compared with current smokers.

Disease-related factors were collected upon inclusion (symptom duration) or updated on indication (current therapy and history of anterior uveitis, IBD, and/or PsO), and bDMARDs and tsDMARDs were grouped.

Outcomes. Indicators of residual disease were fatigue (primary outcome); pain; physical functioning; enthesitis, dactylitis, or peripheral arthritis; health-related quality of life (HRQOL); physician global assessment (PhGA) of disease activity; and acceptance of current state according to patient and physician (Supplementary Table S1, available with the online version of this article).

Fatigue (range 0-10) was assessed with the first item of the Bath Ankylosing Spondylitis Disease Activity Index.[23-25] Pain (axSpA-related, occurring within the past week) was assessed with a visual analog scale (VAS, range 0-10). Physical functioning (range 0-10) was measured with the Bath Ankylosing Spondylitis Functional Index (BASFI).[26] As validated thresholds for these indicators were lacking, fatigue, pain, and BASFI scores > 2/10 and > 4/10 were considered clinically relevant. Clinical inflammation included peripheral arthritis, enthesitis, and dactylitis (swollen joint count [SJC, range 0-66] and tender joint count [range 0-68], entheses [range 0-65], and digits [range 0-20]), and was assessed by a physician. Presence of any swollen joints, enthesitis, or dactylitis (count ≥ 1) was considered relevant clinical inflammation.

HRQOL was measured with the generic 36-item Short Form Health Survey (SF-36), the EuroQoL-5 Dimension questionnaire (EQ-5D) VAS, and the disease-specific Assessment of SpondyloArthritis international Society Health Index (ASAS HI, range 0-17).[27-29] The SF-36 was summarized in a physical component summary (PCS) and mental component summary (MCS; range 0-100), with PCS and MCS scores < 40/100 considered as a relevant impairment in HRQOL.[30] ASAS HI–based health states are as follows: good (ASAS HI ≤ 5), moderate (5 < ASAS HI < 12), and poor (ASAS HI ≥ 12).[31] The rheumatologist's assessment of disease activity was captured with a single VAS (PhGA, range 0-10), with scores > 2/10 indicating relevant disease activity. Finally, acceptance of the current health state was used as an indicator of residual disease, and was assessed with the Patient Acceptable Symptom State (PASS). PASS is a single question for patients and physicians, asking whether it would be acceptable if the patient's current disease state remained unchanged for the next months. PASS was added to SpA-Net in June 2020, several years after its initial launch.

For all measurements, except SF-36 PCS and MCS and EQ-5D VAS, higher scores indicated a worse outcome. The fatigue item, pain VAS, PASS, and PhGA were completed during every visit in SpA-Net, whereas the ASAS HI was completed every 3 months and BASFI, SF-36, and EQ-5D were completed every 6 months (depending on the frequency of rheumatologist visits). Joint, enthesitis, and dactylitis counts were completed on indication.

Statistical analysis. Patient and disease characteristics were described for the overall population and by disease activity state. Next, within the group of patients in an LDA state, the severity and prevalence of indicators of residual disease were described (for LDA and separately for remission and nonremission LDA). The following thresholds were used to identify clin-

ically relevant disease: > 2/10 and > 4/10 for fatigue, pain, and BASFI; < 40/100 for SF-36 PCS and MCS; > 5/17 for ASAS HI; SJC, enthesitis, and dactylitis count ≥ 1; and PhGA > 2/10.

For regression analyses, patients in remission and nonremission LDA were grouped because of sample size. Linear regression analyses were conducted to assess whether sex was associated with severity of residual disease. Other potential explanatory factors were education, employment, smoking, history of EMMs, and current medication (all binary), as well as age and symptom duration (both continuous). Each continuous outcome (fatigue, pain, physical functioning, HRQOL, PhGA) was explored in a separate regression analysis. First, all potential explanatory factors (including sex) were tested in univariable analysis. Second, if sex was potentially associated with the outcome ($P < 0.20$), this was further tested in a multivariable model. Starting with sex, other explanatory factors potentially associated with the outcome ($P < 0.20$ in univariable analysis) were added consecutively to the model in a prespecified order. Factors were retained if they were significant ($P < 0.05$) when entered in this model or if they were a confounder (changed the coefficient of sex by > 10%). Notably, if sex was not potentially associated with an outcome, no multivariable analysis was conducted.

Factors associated with the presence of residual disease were investigated with logistic regression analyses. These analyses were conducted for all binary outcomes (fatigue, pain, and physical functioning [BASFI] scores > 4/10 or > 2/10; HRQOL score < 40/100 [SF-36] or > 5/17 [ASAS HI]; presence of peripheral symptoms; acceptance of current state; and PhGA > 2/10). The same modeling strategy was used as for linear regression.

Four sensitivity analyses were conducted. First, regression analyses were repeated with ASDAS state (remission vs nonremission LDA) as a covariable in the model. Second, the analysis of the primary outcome (fatigue) was repeated in those who were in LDA at ≥ 2 consecutive visits with ≥ 3 months between (persistent LDA). Third, the analysis of the primary outcome was repeated in patients who had none of the other outcomes missing (completers; missing PASS was allowed, as this was later introduced in SpA-Net). Fourth, a manual backward method was explored (starting with all variables with $P < 0.20$ in univariable analysis, eliminating nonsignificant variables one by one) to account for potential suppressor effects. Missing data were not imputed. Interactions were tested and, if significant, analyses were stratified. $P < 0.05$ was considered statistically significant. Analyses were performed in Stata 14.2 (StataCorp).

RESULTS

Population characteristics. In total, 396 patients were included (Supplementary Table S2 and Supplementary Figure, available with the online version of this article). Of these, 267 patients (67.4%) were in an LDA state at some point during follow-up and were included in the LDA subgroup (186/267 [69.7%] nonremission LDA, 81/267 [30.3%] remission; Table 1). The remaining 129 were never in an LDA state during follow-up, constituting the HDA subgroup. In the total population, mean age was 50.6 (SD 14.4) years and 169 patients (42.7%) were female (Supplementary Table S2). The majority were HLA-B27 positive (75.5%), the mean ASDAS was 2.1 (SD 0.9), and about half were on bDMARD treatment. In the LDA and HDA subgroups, most patient characteristics were similar, although patients in LDA were more often highly educated and employed (Supplementary Table S2). Within the LDA group, patients in remission (ASDAS < 1.3), compared to those not in remission (1.3 ≤ ASDAS < 2.1), were less likely to be female (25.9% vs 42.5%, Table 1).

Prevalence of residual disease. Of 267 patients in the LDA subgroup, 218 (81.7%) had ≥ 1 indicator of residual disease. Fatigue was particularly prevalent (n = 177 [66.3%] and n = 114 [42.7%] patients had scores of > 2/10 and > 4/10, respectively; Table 2). Pain and limitations in physical function (> 4/10) were present in approximately 1 in 6 patients. A quarter of patients had reduced physical HRQOL (SF-36 PCS < 40/100), or moderate or poor disease-specific HRQOL (ASAS HI > 5/17). Patients with ≥ 1 indicator of residual disease often had multiple indicators (Figure 1). Nonetheless, the majority of patients and their physicians considered the current state of the patient as acceptable (PASS-patient 88.8%, PASS-physician 97.1%).

Within the LDA subgroup, 54/81 of those in remission and 164/186 of those in nonremission LDA had ≥ 1 indicator of residual disease. Again, fatigue was particularly prevalent (Figure 2).

When comparing the prevalence of the different indicators by sex (primary explanatory factor), prevalence was consistently higher in females (Table 2). Differences were especially striking for fatigue (> 4/10: 54% of females vs 35.9% of males), peripheral symptoms (21.2% vs 4.5%), and physical HRQOL (SF-36 PCS < 40/100: 38% vs 19%; ASAS HI > 5/17: 44.4% vs 24.2%; Table 2).

Factors explaining residual disease. Full regression results are shown in Supplementary Tables S3-23 (available with the online version of this article). In univariable linear regression analyses, sex was potentially associated ($P < 0.20$) with severity of fatigue, ASAS HI, SF-36 PCS, and PhGA. In addition, due to interaction, analyses were stratified for pain and for BASFI. Sex was potentially associated ($P < 0.20$) with pain in nonemployed patients (but not in employed patients), and with BASFI in patients with a history of PsO (but not in patients without a history of PsO; Table 3). In multivariable linear regression analyses, the association between sex and these indicators of residual disease was maintained. Females had significantly worse levels of fatigue (B 0.78, 95% CI 0.18-1.38), pain (B 1.48, 95% CI 0.46-2.51 [nonemployed patients only]), ASAS HI (B 1.91, 95% CI 0.99-2.82), SF-36 PCS (B −3.55, 95% CI −5.82 to −1.28), and PhGA (B 0.38, 95% CI 0.04-0.72; Table 3). No associations were observed between sex and mental HRQOL or EQ-5D VAS in linear regression.

Several other factors were associated with the severity of residual disease. Higher age was associated with less fatigue but worse PhGA; being employed with better ASAS HI and SF-36 PCS; a history of IBD with worse fatigue ASAS HI and SF-36 PCS; current use of NSAIDs with better ASAS HI; and bDMARDs with worse fatigue (Supplementary Tables S3-10, available with the online version of this article).

Logistic regression analysis of the presence of clinically relevant residual disease yielded similar results (Table 4). In univariable logistic regression analysis, sex was potentially associated ($P < 0.20$) with presence of fatigue, pain, moderate-to-poor ASAS HI, and PASS-patient (in the total population), as well as with high BASFI (employed subgroup only) and presence of peripheral symptoms (low education subgroup only). In multivariable analyses, most of these associations were maintained (Table 4). Females were significantly more likely to have fatigue

Table 1. Population characteristics in the overall LDA group and by remission or nonremission state.

	Remission and Nonremission LDA, n = 267	Remission, ASDAS < 1.3, n = 81	Nonremission LDA, 1.3 ≤ ASDAS < 2.1, n = 186
Age, yrs	50.6 (14.3)	49.9 (15.8)	50.9 (13.7)
Female, n (%)	100 (37.5)	21 (25.9)	79 (42.5)
Higher education, n (%)	85 (41.1)	30 (44.1)	55 (39.6)
Employed, n (%)	129 (61.7)	48 (70.6)	81 (57.4)
Smoking, n (%)			
Never	91 (44.6)	30 (44.8)	61 (44.5)
Former	73 (35.8)	24 (35.8)	49 (35.8)
Current	40 (19.6)	13 (19.4)	27 (19.7)
Fulfills ASAS axSpA classification criteria, n (%)	230 (86.1)	70 (86.4)	160 (86)
Symptom duration, yrs	20.6 (13.6)	22.0 (12.7)	20.0 (14)
HLA-B27 positive, n (%)	176 (75.5)	55 (78.6)	121 (74.2)
EMMs, n (%)			
History of uveitis	66 (25.5)	16 (20.3)	50 (27.8)
History of PsO	36 (13.9)	6 (7.6)	30 (16.7)
History of IBD	29 (11.2)	4 (5.1)	25 (13.9)
Current medication use, n (%)			
NSAID	119 (44.6)	39 (48.1)	80 (43.0)
csDMARD	24 (9)	6 (7.4)	18 (9.7)
bDMARD	145 (54.3)	44 (54.3)	101 (54.3)
tsDMARD	(0)	0 (0)	0 (0)
ASDAS, 0-∞	1.5 (0.4)	1.0 (0.3)	1.8 (0.2)
BASDAI, 0-10	2.7 (1.4)	1.7 (1.0)	3.2 (1.3)
CRP, mg/L, 0-∞	2.9 (3.6)	1.7 (1.2)	3.5 (4.1)
PtGA, 0-10	2.3 (1.6)	1.2 (1.0)	2.8 (1.7)
Fatigue, 0-10	4.0 (2.5)	3.1 (2.3)	4.5 (2.4)
Pain, 0-10	2.3 (1.9)	1.5 (1.8)	2.7 (1.8)
BASFI, 0-10	2.4 (2.0)	1.4 (1.3)	2.8 (2.1)
ASAS HI, 0-17	4.2 (3.3)	2.8 (2.6)	4.8 (3.4)
EQ-5D VAS, 0-100	66.0 (23.0)	68.0 (25.3)	65.1 (22.0)
SF-36 PCS, 0-100	45.2 (7.9)	48.5 (7.5)	43.6 (7.6)
SF-36 MCS, 0-100	51.3 (10.3)	51.8 (9.4)	51.0 (10.8)
PASS, patient, n (%)	71 (88.8)	26 (96.3)	45 (84.9)
PASS, physician, n (%)	66 (97.1)	23 (95.8)	43 (97.7)
PhGA, 0-10	1.3 (1.0)	1.0 (0.9)	1.5 (1.0)
SJC ≥ 1, n (%)	5 (3)	0 (0)	5 (4.3)
TJC ≥ 1, n (%)	14 (8.5)	3 (6.1)	11 (9.6)
Dactylitis, presence, n (%)	1 (0.6)	0 (0)	1 (0.8)
Enthesitis, presence, n (%)	13 (7.3)	2 (3.8)	11 (8.8)

Values expressed as mean (SD) unless otherwise stated. ASAS: Assessment of SpondyloArthritis international Society; ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biological disease-modifying antirheumatic drug; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; EMM: extramusculoskeletal manifestation; EQ-5D: EuroQoL-5 Dimension questionnaire; IBD: inflammatory bowel disease; LDA: low disease activity; MCS: mental component summary; NSAID: nonsteroidal antiinflammatory drug; PASS: patient acceptable symptom state; PCS: physical component summary; PhGA: physician global assessment; PsO: psoriasis; PtGA: patient global assessment; SF-36: 36-item Short Form Health Survey; SJC: swollen joint count; TJC: tender joint count; tsDMARD: targeted synthetic disease-modifying antirheumatic drug; VAS: visual analog scale.

(> 4/10: odds ratio [OR] 3.29, 95% CI 1.74-6.20), pain (> 4/10: OR 2.81, 95% CI 1.24-6.38), high BASFI (> 4/10: OR 7.06, 95% CI 1.33-37.62 [employed only]), peripheral symptoms (OR 24.69, 95% CI 2.89-210.99 [low education only]), moderate or poor ASAS HI (OR 2.72, 95% CI 1.35-5.46), and reduced physical HRQOL (OR 2.67, 95% CI 1.33-5.36). No associations were observed between sex and mental HRQOL, PASS, or PhGA in logistic regression.

Table 2. Residual disease in patients with LDA (ASDAS < 2.1).

	All, n = 267	Female Sex, n = 100	Male Sex, n = 167
Fatigue > 2/10	177 (66.3)	69 (69)	108 (64.7)
Fatigue > 4/10	114 (42.7)	54 (54)	60 (35.9)
Pain > 2/10	95 (49.7)	46 (60.5)	49 (42.6)
Pain > 4/10	34 (17.8)	19 (25)	15 (13)
BASFI > 2/10	115 (49.4)	49 (54.4)	66 (46.2)
BASFI > 4/10	41 (17.6)	16 (17.8)	25 (17.5)
Peripheral symptoms, excluding tender joints	18 (11.6)	14 (21.2)	4 (4.5)
Enthesitis, any	13 (7.3)	9 (12.2)	4 (3.8)
Dactylitis, any	1 (0.6)	1 (1.4)	(0)
Swollen joints, any	5 (3)	5 (7.4)	(0)
Tender joints, any	14 (8.5)	5 (7.4)	9 (9.4)
SF-36 PCS < 40/100	47 (26.7)	27 (38)	20 (19)
SF-36 MCS < 40/100	30 (17)	13 (18.3)	17 (16.2)
ASAS HI ≥ 12/17 (poor)	5 (2.9)	4 (5.6)	1 (1)
ASAS HI > 5/17 (moderate/poor)	56 (32.7)	32 (44.4)	24 (24.2)
PASS, patient	71 (88.8)	27 (81.8)	44 (93.6)
PASS, physician	66 (97.1)	28 (96.6)	38 (97.4)
PhGA > 2/10	26 (16.4)	10 (15.9)	16 (16.7)
PhGA > 4/10	1 (0.6)	0 (0)	1 (1)

Values are expressed as n (%). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; LDA: low disease activity; MCS: mental component summary; PASS: patient acceptable symptom state; PCS: physical component summary; PhGA: physician global assessment; SF-36: 36-item Short Form Health Survey.

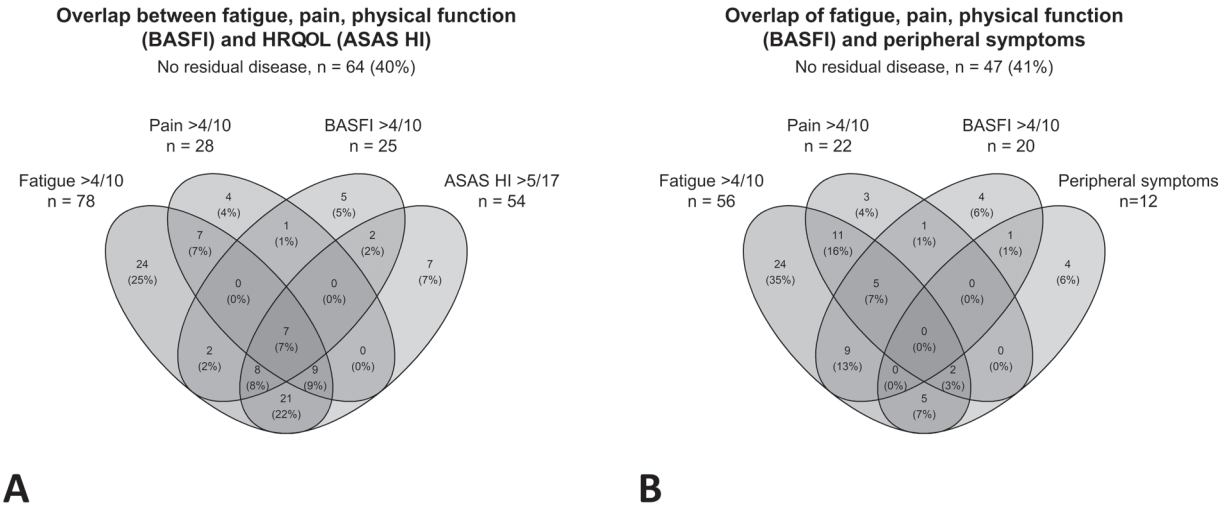

Figure 1. Relationship and overlap between indicators of residual disease. Number and percentage of patients with residual disease (note: not all indicators of residual disease are shown). The percentages in the diagrams are based on the population of patients that had ≥ 1 of the indicators of residual disease included in the diagram. For the indicators of residual disease shown in Figure 1A, 97 patients (60% of total) had ≥ 1 indicator and 57 patients (35% of total, 59% of those with ≥ 1 indicator) had ≥ 2 indicators. For the indicators of residual disease shown in Figure 1B, 69 patients (61% of total) had ≥ 1 indicator and 34 patients (30% of total, 49% of those with ≥ 1 indicator) had ≥ 2 indicators. ASAS HI: Assessment of SpondyloArthritis international Society Health Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HRQOL: health-related quality of life.

Several factors were associated with the prevalence of residual disease. Higher age was associated with less frequent fatigue and reduced SF-36 PCS; being employed with less frequent pain; a history of IBD with more frequent fatigue and worse ASAS HI; a history of PsO with more frequent impaired physical function (BASFI); and current use of NSAIDs with more frequent peripheral involvement (Supplementary Tables S11-23, available with the online version of this article).

Sensitivity analyses. The sensitivity analyses confirmed the results of the main analyses. Additional adjustment for ASDAS state

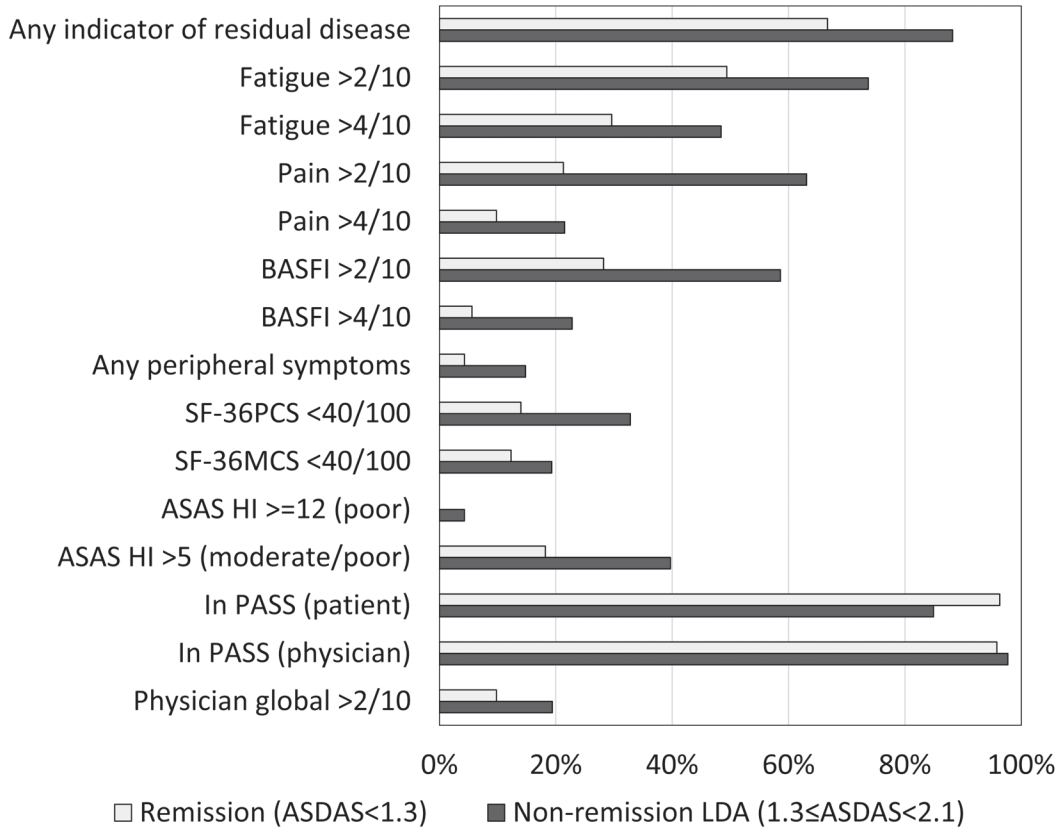

Figure 2. Residual disease indicators in patients with ASDAS < 2.1 by disease activity state. For all outcomes, except PASS, a higher percentage reflects higher prevalence of residual disease. ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; LDA: low disease activity; MCS: mental component summary; PASS: patient acceptable symptom state; PCS: physical component summary; SF-36: 36-item Short Form Health Survey.

(remission vs nonremission LDA) slightly reduced the strength of association for some outcomes but still yielded clinically relevant and statistically significant associations between sex and residual disease (Supplementary Table S24 and Supplementary Table S25, available with the online version of this article). Analyses in those with ASDAS < 2.1 at 2 consecutive visits (persistent LDA) and those who had all outcomes nonmissing (completers) also led to similar results (Supplementary Tables S26-32). Finally, using a backward instead of a forward method resulted in similar results (and often the exact same models; data not shown).

DISCUSSION

In our observational study, a wide variety of indicators of residual disease, including patient-reported and physician-reported indicators, were prevalent in a substantial proportion of patients with axSpA who were in an LDA state (ASDAS < 2.1), including patients who were in remission (ASDAS < 1.3). Most indicators of residual disease were both more frequent and more severe in female patients compared to male patients, independent of other explanatory factors. This included specific symptoms such as pain and fatigue, but also the broader experience of HRQOL (functioning and health).

In axSpA, 2 studies that we know of have investigated residual disease in patients with axSpA.[11,15] The reported prevalence of residual symptoms was similar to that which we observed. In one of these studies, female patients were more likely to experience fatigue (but not pain), but these were unadjusted analyses.[15] In our study, for the first time in axSpA, we explored which factors were associated with different indicators of residual disease while also accounting for confounders. Sex explained both the prevalence and severity of residual disease. Our observations fit within the sex/gender disparity in axSpA. Female patients typically have a longer delay in diagnosis, report worse scores on patient-reported outcome measures, and have a lower treatment response, whereas male patients tend to have higher levels of CRP and more progression of structural damage.[16,17,32,33] We can only speculate on potential explanations for our observations. Female patients with axSpA might have a different phenotype, resulting in certain symptoms being more dominant when compared to male patients.[34] Alternatively, female and male patients might experience (or report) their symptoms differently. Pain mechanisms, for example, are influenced by sex hormones, and females and males differ in the number and expression of pain receptors.[17] Sex differences in psychological and social context could also affect symptom

Table 3. Associations between sex and residual disease in univariable and multivariable linear regression models in patients with ASDAS < 2.1.

Outcome	Sex, Female vs Male						Covariables in Multivariable Model
	Univariable Regression			Multivariable Regression			
	B_{sex}	95% CI	*P*	B_{sex}	95% CI	*P*	
Fatigue, 0-10	0.81	0.20 to 1.42	< 0.01	0.78	0.18 to 1.38	0.01	Age[a], IBD[a], b/tsDMARD[a], PsO[b], csDMARD[b]
Pain, 0-10[c]	1.67	0.66 to 2.68	< 0.01	1.48	0.46 to 2.51	< 0.01	PsO[a], IBD[b], csDMARD[b], b/tsDMARD[b]
BASFI, 0-10[c]	1.64	−0.10 to 3.37	0.06	N/A[d]	N/A	N/A	N/A[d]
ASAS HI, 0-17	1.90	0.93 to 2.88	< 0.01	1.91	0.99 to 2.82	< 0.01	Employed[a], IBD[a], NSAID[a], PsO[b]
SF-36 PCS, 0-100	−3.67	−6.02 to −1.33	< 0.01	−3.55	−5.82 to −1.28	< 0.01	Age[a], employed[a], IBD[a], PsO[b], NSAID[b]
SF-36 MCS, 0–100	0.46	−2.68 to 3.61	0.77	N/A	N/A	N/A	N/A
EQ-5D VAS, 0-100	−1.28	−11.19 to 8.64	0.80	N/A	N/A	N/A	N/A
PhGA, 0-10	0.33	0.01 to 0.65	0.04	0.38	0.04 to 0.72	0.03	Age[a], education[a], employed[b], symptom duration[c], PsO[b]

Each outcome was assessed in a separate regression model. Full results of each multivariable linear regression model, including coefficients of potential covariables in univariable and multivariable analysis, are shown in Supplementary Tables S3-10. For all outcomes, except SF-36 PCS/MCS and EQ-5D, $B_{sex} > 0$ indicates more severe residual disease in females. N/A was used when no multivariable regression was conducted, because sex was not potentially associated with the outcome in univariable analysis. [a]Retained in final model (statistically significant association with outcome and/or confounder for sex). [b]Tested in multivariable model, but not retained (not associated with the outcome and no confounder for sex). [c]In subgroup of patients (stratified analysis due to interaction with sex): currently not employed (outcome = pain), history of PsO (outcome = BASFI). [d]Although there was a potential association between sex and the outcome in univariable analysis in the subgroup of patients with a history of PsO, no multivariable regression analysis was conducted due to the small sample size of this subgroup (n = 31). [e]Potentially associated with the outcome but not included in multivariable model due to collinearity with age (age preferred due to fewer missing data). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; b/tsDMARD: biological or targeted synthetic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; EQ-5D: EuroQoL-5 Dimension questionnaire; IBD: inflammatory bowel disease; MCS: mental component summary; N/A: not applicable; NSAID: nonsteroidal antiinflammatory drug; PCS: physical component summary; PhGA: physician global assessment; PsO: psoriasis; SF-36: 36-item Short Form Health Survey; VAS: visual analog scale.

experience.[35] Further, female patients may be relatively undertreated. In support of this, female patients were more likely to have physician-assessed peripheral symptoms, in line with other studies.[34] In addition, male patients were more likely to be in remission (ASDAS < 1.3) compared to female patients in our study. This could indicate that, even though these female patients have already achieved a low level of disease activity, there might still be room for further improvement of their disease state.

Regardless of the underlying mechanisms, residual disease is relevant for daily practice. Not all patients can achieve remission, and nonremission LDA is considered an alternative target.[10,36] One might expect some remaining disease burden in patients who are in a nonremission LDA state as they are, by definition, not in remission; however, we demonstrate that most of these patients have clinically relevant symptoms. Further, even among those who are actually in remission, over half of patients experienced some form of residual disease. Not only did we observe specific residual symptoms such as pain or fatigue, but the broader outcome of HRQOL was also affected. Interestingly, despite these symptoms, almost 90% of patients considered themselves to be in an acceptable symptom state. Adaptation might play a role here, and an acceptable state likely differs from the optimal one.

Our observations also suggest that some aspects of the disease are not (sufficiently) captured by the ASDAS, or that the endorsed cut-offs are not fit for daily practice. For example, a history of EMMs was associated with several indicators, and it might be that some of these patients still experience symptom or disease burden due to EMMs. We should emphasize that this does not necessarily mean that the ASDAS is not a good measure or target for disease management. Part of our study population already had established disease, and using ASDAS targets in early axSpA might lead to less residual disease. However, our results do suggest that other targets might need to be considered as well. Finally, one-third of patients in our cohort did not achieve an ASDAS < 2.1 at any point during follow-up (the HDA group), highlighting another challenging issue in daily practice.

Our study has several strengths. SpA-Net is a daily practice registry. We were able to investigate residual disease in the whole spectrum of axSpA, and the results are likely generalizable. In addition, despite a lack of instruments specifically designed to assess residual disease, we used validated measures for most outcomes. As established thresholds for (residual) fatigue, pain, and limitations in physical functioning are lacking, we included a strict threshold of 4/10 to be specific, yet we also explored a lower threshold of 2/10 for comparative purposes.[11] Of note, none of these thresholds were validated. Due to the broad range of patient-reported and physician-assessed outcomes collected in SpA-Net, we could investigate a wide variety of potentially relevant indicators for residual disease.

Our current study also has limitations. First, as this was a cross-sectional study, no firm conclusions can be drawn regarding causality. Notably, our primary explanatory factor (sex), as well as several secondary factors, were fixed over time.

Table 4. Associations between sex and residual disease in univariable and multivariable logistic regression models in patients with ASDAS < 2.1.

Outcome	Sex, Female vs Male						Covariables in Multivariable Model
	Univariable Regression			Multivariable Regression			
	OR_{sex}	95% CI	*P*	OR_{sex}	95% CI	*P*	
Fatigue > 4/10	2.09	1.26-3.47	< 0.01	3.29	1.74-6.20	< 0.001	Symptom duration[a], IBD[b], PsO[b]
Fatigue > 2/10[c]	2.30	1.03-5.16	0.04	2.28	0.97-5.33	0.06	Age[a], IBD[a], symptom duration[d], smoking[b]
Pain > 4/10	2.22	1.05-4.71	0.04	2.81	1.24-6.38	0.01	Employed[a], smoking[b], uveitis[b], PsO[b]
Pain > 2/10	2.07	1.14-3.73	0.02	2.80	1.45-5.42	< 0.01	Employed[a], smoking[a], IBD[b]
BASFI > 4/10[c]	6.45	1.31-31.79	0.02	7.06	1.33-37.62	0.02	PsO[a], age[b], IBD[b]
BASFI > 2/10	1.39	0.82-2.37	0.22	N/A	N/A	N/A	N/A
Peripheral symptoms[c]	22.00	2.69-179.61	< 0.01	24.69	2.89-210.99	< 0.01	NSAID[a], csDMARD[b]
ASAS HI > 5/17	2.50	1.30-4.81	< 0.01	2.72	1.35-5.46	< 0.01	Employed[a], IBD[a], NSAID[b]
SF-36 PCS < 40/100	2.61	1.32-5.16	< 0.01	2.67	1.33-5.36	< 0.01	Age[a], employed[b], IBD[b], PsO[b], csDMARD[b]
SF-36 MCS < 40/100	1.16	0.52-2.57	0.71	N/A	N/A	N/A	N/A
PASS patient	0.31	0.07-1.33	0.11	0.31	0.07-1.33	0.11	None
PASS physician	0.74	0.04-12.29	0.83	N/A	N/A	N/A	N/A
PhGA > 2/10	0.94	0.40-2.24	0.89	N/A	N/A	N/A	N/A

Each outcome was assessed in a separate regression model. Full results of each multivariable logistic regression model, including coefficients of potential covariables in univariable and multivariable analysis, are shown in Supplementary Tables S11-23. For all outcomes except PASS, OR > 1 indicates a higher probability of residual disease in females. N/A was used when no multivariable regression was conducted, because sex was not potentially associated with the outcome in univariable analysis. [a]Retained in final model (statistically significant association with outcome and/or confounder for sex). [b]Tested in multivariable model, but not retained (not associated with the outcome and no confounder for sex). [c]In subgroup of patients (stratified analysis due to interaction with sex): currently not on NSAIDs (outcome = fatigue > 2/10), currently employed (outcome = BASFI > 4/10), low education (outcome = peripheral symptoms). [d]Potentially associated with the outcome but not included in multivariable model due to collinearity with age (age preferred due to fewer missing data). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; IBD: inflammatory bowel disease; MCS: mental component summary; N/A: not applicable (no multivariable regression was conducted, because sex was not potentially associated with the outcome in univariable analysis); NSAID: nonsteroidal antiinflammatory drug; OR: odds ratio; PASS: patient acceptable symptom state; PCS: physical component summary; PhGA: physician global assessment; PsO: psoriasis; SF-36: 36-item Short Form Health Survey.

Second, because of limited sample size, we grouped patients in remission and nonremission LDA in the regression analyses. Third, for most outcomes, there were missing data; however, for the primary outcome (fatigue), data were complete, and a completer analysis led to similar results. Fourth, although we had data on several patient and disease-related factors that could explain residual disease, it is possible that residual confounding occurred. For example, information on psychological factors was unavailable.

In conclusion, in clinical practice most patients in an LDA state (including remission) have residual disease, and female patients are more likely to report this. Future studies should address how to best understand and manage residual disease in order to optimize the short-term and long-term health of all patients with axSpA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390:73-84.
2. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82:19-34.
3. Boonen A, Sieper J, van der Heijde D, et al. The burden of non-radiographic axial spondyloarthritis. Semin Arthritis Rheum 2015;44:556-62.
4. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. J Rheumatol Suppl 2006;78:4-11.
5. Machado P, Landewé R, Braun J, et al. A stratified model for health outcomes in ankylosing spondylitis. Ann Rheum Dis 2011; 70:1758-64.
6. Ramiro S, van der Heijde D, van Tubergen A, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis 2014;73:1455-61.
7. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978-91.
8. Machado PM, Landewé R, Heijde DV, Assessment of SpondyloArthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis 2018;77:1539-40.
9. Beckers E, Boonen A, Webers C, et al. Treat-to-target in axial spondyloarthritis: an observational study in daily practice. Rheumatology 2022;61:1396-407.
10. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77:3-17.
11. Liu V, Fong W, Kwan YH, Leung YY. Residual disease burden in patients with axial spondyloarthritis and psoriatic arthritis despite

low disease activity states in a multiethnic Asian population. J Rheumatol 2021;48:677-84.
12. Michaud K, Pope J, van de Laar M, et al. Systematic literature review of residual symptoms and an unmet need in patients with rheumatoid arthritis. Arthritis Care Res 2021;73:1606-16.
13. van Mens LJJ, Turina MC, van de Sande MGH, Nurmohamed MT, van Kuijk AWR, Baeten DLP. Residual disease activity in psoriatic arthritis: discordance between the rheumatologist's opinion and minimal disease activity measurement. Rheumatology 2018; 57:283-90.
14. Mulder MLM, van Hal TW, van den Hoogen FHJ, de Jong EMGJ, Vriezekolk JE, Wenink MH. Measuring disease activity in psoriatic arthritis: PASDAS implementation in a tightly monitored cohort reveals residual disease burden. Rheumatology 2021;60:3165-75.
15. D'Angelo S, Salvarani C, Marando F, et al. Residual disease in patients with axial spondyloarthritis: a post-hoc analysis of the QUASAR study. J Clin Med 2022;11.
16. Webers C, Essers I, Ramiro S, et al. Gender-attributable differences in outcome of ankylosing spondylitis: long-term results from the Outcome in Ankylosing Spondylitis International Study. Rheumatology 2016;55:419-28.
17. Rusman T, van Bentum RE, van der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. Rheumatology 2020;59 Suppl 4:iv38-46.
18. Webers C, Beckers E, Boonen A, et al. Development, usability and acceptability of an integrated ehealth system for spondyloarthritis in the Netherlands (SpA-Net). RMD Open 2019;5:e000860.
19. Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18-24.
20. Machado P, Landewé R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47-53.
21. Machado PM, Landewé RB, van der Heijde DM. Endorsement of definitions of disease activity states and improvement scores for the Ankylosing Spondylitis Disease Activity Score: results from OMERACT 10. J Rheumatol 2011;38:1502-6.
22. Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment questionnaire in ankylosing spondylitis. Rheumatology 2010;49:812-9.
23. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
24. van Tubergen A, Coenen J, Landewé R, et al. Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. Arthritis Rheum 2002;47:8-16.
25. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of spondyloarthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl 2:ii1-44.
26. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
27. Kiltz U, van der Heijde D, Boonen A, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis 2015;74:830-5.
28. Ware JE Jr., Sherbourne CD, the MOS. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
29. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208 [DOI: 10.1016/0168-8510(90)90421-9].
30. Revicki DA, Rentz AM, Luo MP, Wong RL. Psychometric characteristics of the short form 36 health survey and functional assessment of chronic illness therapy-fatigue subscale for patients with ankylosing spondylitis. Health Qual Life Outcomes 2011;9:36.
31. Kiltz U, van der Heijde D, Boonen A, et al. Measurement properties of the ASAS Health Index: results of a global study in patients with axial and peripheral spondyloarthritis. Ann Rheum Dis 2018;77:1311-7.
32. Garrido-Cumbrera M, Navarro-Compán V, Bundy C, et al. Identifying parameters associated with delayed diagnosis in axial spondyloarthritis: data from the European map of axial spondyloarthritis. Rheumatology 2022;61:705-12.
33. Chimenti MS, Alten R, D'Agostino MA, et al. Sex-associated and gender-associated differences in the diagnosis and management of axial spondyloarthritis: addressing the unmet needs of female patients. RMD Open 2021;7.
34. Mease PJ, McLean RR, Dube B, et al. Comparison of men and women with axial spondyloarthritis in the US-based Corrona psoriatic arthritis/spondyloarthritis registry. J Rheumatol 2021;48:1528-36.
35. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and pain perception - Part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? Pain 2012;153:619-35.
36. Molto A, López-Medina C, Van den Bosch FE, et al. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. Ann Rheum Dis 2021;80:1436-44.