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ORIGINAL ARTICLE

Spectrum of ankylosing spondylitis in Portugal. Development of BASDAI, BASFI, BASMI and mSASSS reference centile charts

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Abstract The availability of population-specific normative data regarding disease severity measures is essential for patient assessment. The goals of the current study were to characterize the pattern of ankylosing spondylitis (AS) in Portuguese patients and to develop reference centile charts for BASDAI, BASFI, BASMI and mSASSS, the most widely used assessment tools in AS. AS cases were recruited from hospital outpatient clinics, with AS defined according to the modified New York criteria. Demographic and clinical data were recorded. All radiographs were evaluated by two independent experienced readers. Centile charts for BASDAI, BASFI, BASMI and mSASSS were constructed for both genders, using generalized linear models and regression models with duration of disease as independent variable. A total of 369 patients (62.3% male, mean±(SD) age 45.4±13.2 years, mean±(SD) disease duration 11.4±10.5 years, 70.7% B27-positive) were included. Family history of AS in a first-degree relative was reported in 17.6% of the cases. Regarding clinical disease pattern, at the time of assessment 42.3% had axial disease, 2.4% peripheral disease, 40.9% mixed disease and 7.1% isolated enthesopatic disease. Anterior uveitis

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(33.6%) was the most common extra-articular manifestation. The centile charts suggest that females reported greater disease activity and more functional impairment than males but had lower BASMI and mSASSS scores. Data collected through this study provided a demographic and clinical profile of patients with AS in Portugal. The development of centile charts constitutes a useful tool to assess the change of disease pattern over time and in response to therapeutic interventions.

Keywords Ankylosing spondylitis · Charts · Epidemiology

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by inflammation in the spine and sacroiliac joints leading to progressive joint ankylosis. Peripheral joints and entheses are frequently involved, and inflammation may involve extra-articular sites such as the uvea, aorta, heart, lungs and kidneys. AS is a common cause of inflammatory arthritis worldwide, with a prevalence of 0.2–0.9% in white European populations [1], but its aetiology is still incompletely understood. AS typically affects young people, with symptoms onset usually occurring in the early 20s, leading to progressive deterioration of physical function and quality of life. Work disability is higher in AS patients than expected in the general population, with a remarkable impact on productivity and social costs [2], and there is some evidence of increased mortality [3].

Assessment of disease activity and severity in AS is of clinical utility in determining current disease status, prognosis and the effects of therapeutic interventions. The BASDAI [4] and BASFI [5] self-administered patient questionnaires are the most widely used tools for the assessment of AS activity and functional status. Metrology is also widely used, providing an objective measure of the effects of the disease on joint mobility; the BASMI [6] is generally the scoring tool for AS metrology. Finally, the mSASSS [7] scores radiographic features of AS and is now considered the preferred method for measurement of damage progression in patients with AS. Reference centile charts have been developed for AS British patients for BASDAI, BASFI and BASMI [8], but no published charts are available from any other population. Furthermore, reference centile charts have never been developed for mSASSS in any studied population.

Well characterised differences between ethnic groups regarding clinical manifestations of some other major inflammatory conditions, such as systemic lupus erythematosus [9], have been described, but there is little data about inter-ethnic differences in AS patients. Characterising differences between ethnic groups is an important process, potentially guiding research into determinants of disease manifestations and severity and being of obvious relevance for the clinical management in the different ethnic groups concerned.

The aim of the present study was to characterise AS clinical manifestations in Portuguese AS patients and to construct reference centile charts for BASDAI, BASFI, BASMI and mSASSS in our population.

Materials and methods

We collected cross-sectional data on Portuguese AS patients, between April 2007 and April 2008. Cases were recruited from patients attending outpatient clinics in nine out of 14 hospitals, which are the main rheumatology referral centres in their regions. The hospitals involved represent two thirds of all rheumatology centers operating in the Portuguese Hospital National Health System (NHS). Nationwide, the hospitals participating in our study

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accounted for approximately 75.6% of all rheumatology visits in 2007 in Portugal. These centres were located in seven different cities, including urban and rural zones, and represent a broad socio-demographic spectrum of the population treated by the NHS. The patients were selected consecutively in each center in the 2 months prior to the visit of the interviewers. Four previously trained rheumatologists were responsible for the data collection and physical examination of all patients enrolled in each involved centre. This procedure facilitated a consistent data collection and ensured a high response rate. Written informed consent was obtained from all study participants, and the study was approved by the Ethics Committee of the University Hospital Centro Hospitalar de Lisboa Ocidental, Hospital de Egas Moniz and by the Ethics Board of the involved centres.

Data collection

All patients were selected according to the inclusion criteria: (a) AS defined by the modified New York criteria [10], (b) age above 18 years old, and to the exclusion criteria: (a) other types of spondylarthritis distinct from AS. Patients completed a questionnaire concerning demographic characteristics, disease features and the BASDAI and BASFI questionnaires. Age at disease onset was defined as the age at symptom onset, and disease duration was defined as the period of time (years) after symptoms onset. For the evaluation of the disease status, the following anthropometrical measures included in the Bath Ankylosing Spondylitis Metrological Index (BASMI) were used and performed: tragus-to-wall distance, modified Schober's test, lateral flexion of lumbar spine, cervical rotation and intermalleolar distance. All patients had pelvic x-rays performed confirming the presence of at least grade 2 bilateral, or unilateral grade 3, sacroiliitis. The modified Stoke Ankylosing Spondylitis Severity Score (mSASSS) [7] was determined when cervical and lumbar x-rays were available (n=213); all radiographs were scored independently by two of us (FS, AFM). Where there was discordance between the scores, they were re-evaluated together by both reviewers, and a consensus score was obtained. Laboratory tests including ESR and HLA-B27 status, determined by sequence-specific single-stranded oligonucleotide probes (SSOP), were evaluated in all patients. Current treatments including non-steroidal anti-inflammatory drugs, glucocorticoids, disease-modifying anti-rheumatic drugs and biological therapies were recorded.

Statistical analysis

Descriptive statistics are presented as mean±standard deviation when referring to quantitative variables and in absolute frequencies and percentages when referring to qualitative variables. The non-parametric Mann–Whitney–Wilcoxon test was used to compare groups in the presence of skewed data.

Centile charts, showing the 5th, 10th, 25th, 50th, 75th, 90th and 95th centiles, were estimated for males and females separately using alternative models for mean and standard deviation for each Bath AS indexes and mSASSS.

The centile curves were calculated using the following equation:

$$\text{centile} = \text{mean} + K \times \text{SD}$$

where K is the corresponding centile of the standard Gaussian distribution.

The mean values were estimated by the fitting Generalized Linear Models (GLM) for each Bath AS indexes and mSASSS with disease duration as covariate. We tried to fit the best model according to the data structure. We used the Gamma, Poisson and Gaussian families and log and identity function as link functions. The quality of adjustment was assessed by the residuals analysis.

The standard deviation (SD) was estimated by linear regression using the absolute value of the residuals from the GLM regression multiplied by $\sqrt{\pi/2} = 1.253$ as the dependent variable and the disease duration as the independent variable.

Socio-demographic and clinical determinants of each Bath AS index were investigated by multivariate regression analysis using GLM. Alternative models specification was assessed with the Akaike information criterion (AIC), the Bayesian information criterion (BIC), deviance and Ramsey reset test. Normality tests and residual analyses were done to check the assumptions of models.

Coefficients with p-value <0.05 were considered significant. The statistical analysis was performed with Stata SE 10 software.

Results

Eleven outpatient clinics from seven different cities were involved from mainland Portugal, representing a broad spectrum of the population treated in the Hospitalar Portuguese Health System. A total of 369 patients were included (62.3% men and 37.1% women), with a mean age of 45.4±13.2 years (range 20–79 years). Table 1 shows the average values of disease duration, age of symptom onset, age of diagnosis and diagnosis delay for the whole group and by sex. The mean disease duration was 11.4±10.5 years (range 0–46 years), the mean age of disease onset was 26.5± 10.8 years and the mean age at diagnosis was 34.1± 12.4 years. The mean delay between onset of symptoms

Table 1 Characteristics of the overall cohort and analysis by gender

	Total	Male	Female	*p*-value*
Gender (*n*;(%))	369 (100%)	232 (62.8%)	(137) 37.1%	–
Age (years)	45.4±13.2	45.7±13.5	44.9±13.9	0.52
Age at onset (years)	26.5±10.8	25.8±10.8	27.5±10.8	0.185
Age at diagnosis (years)	34.1±13.4	33.0±12.3	35.8±12.4	0.040
Time of evolution (years)	18.9±12.7	19.8±12.6	17.6±13.0	0.068
Disease duration (years)	11.4±10.5	12.6±11.0	9.5±9.3	0.022
Diagnosis delay (years)	7.6±9.0	7.1±9.0	8.3±9.0	0.081
Patient global assessment(cm)	4.7±2.4	4.3±2.5	4.8±2.3	0.072
Physician global assessment (cm)	2.6±1.9	2.5±1.9	2.6±1.8	0.36
				<0.001[a]
BASDAI	4.2±2.3	3.7±2.2	4.9±2.3	<0.001
BASFI	4.1±2.7	3.8±2.6	4.5±2.7	0.010
BASMI	4.0±2.5	4.3±2.6	3.5±2.2	0.006
mSASSS	20.9±23.1	27.4±24.6	9.8±14.7	<0.001
ESR (mm/h)	21.7±17.7	20.1±17.4	24.3±18.2	0.012
HLA-B27 positivity (*n* positive: *n* total, (%))	290:360 (80.5%)	183:220 (83.2%)	107:140 (76.4%)	–

Mean ± standard deviation

*Mann–Whitney–Wilcoxon test

[a]*t*-test comparison between patient and medical evaluation

and diagnosis was 7.6±9.0 years and was less than 1 year in 51 cases (13.8%) and longer than 10 years in 86 cases (23.3%). There was no difference in the age of symptom onset between males and females (25.8 vs 27.5, $p=0.185$), although males were diagnosed at a slightly earlier age (33.0 vs 35.8 years, $p=0.040$). Juvenile onset (age <16 years) was reported in 39 (10.6%) of cases, whereas late onset (age > 40 years) was reported in 37 (10%). Family history of AS, in a first-degree relative, was reported in 65 of 369 (17.6%) patients.

Lower back pain (42.3%) was the most common initial manifestation. At the time of assessment for this study, 49.9% had axial disease, 2.4% peripheral disease, 40.9% mixed disease and 7.1% isolated enthesopatic disease. Extra-articular manifestations were experienced by 35.2% of the patients, with anterior uveitis (33.6%) being the most common feature. Other associated extra-articular manifestations were less frequent: psoriasis (6.2%), coexistent inflammatory bowel disease (2.4%), pulmonary disease (1.4%), cardiac disease (1.1%) and renal disease (0.3%).

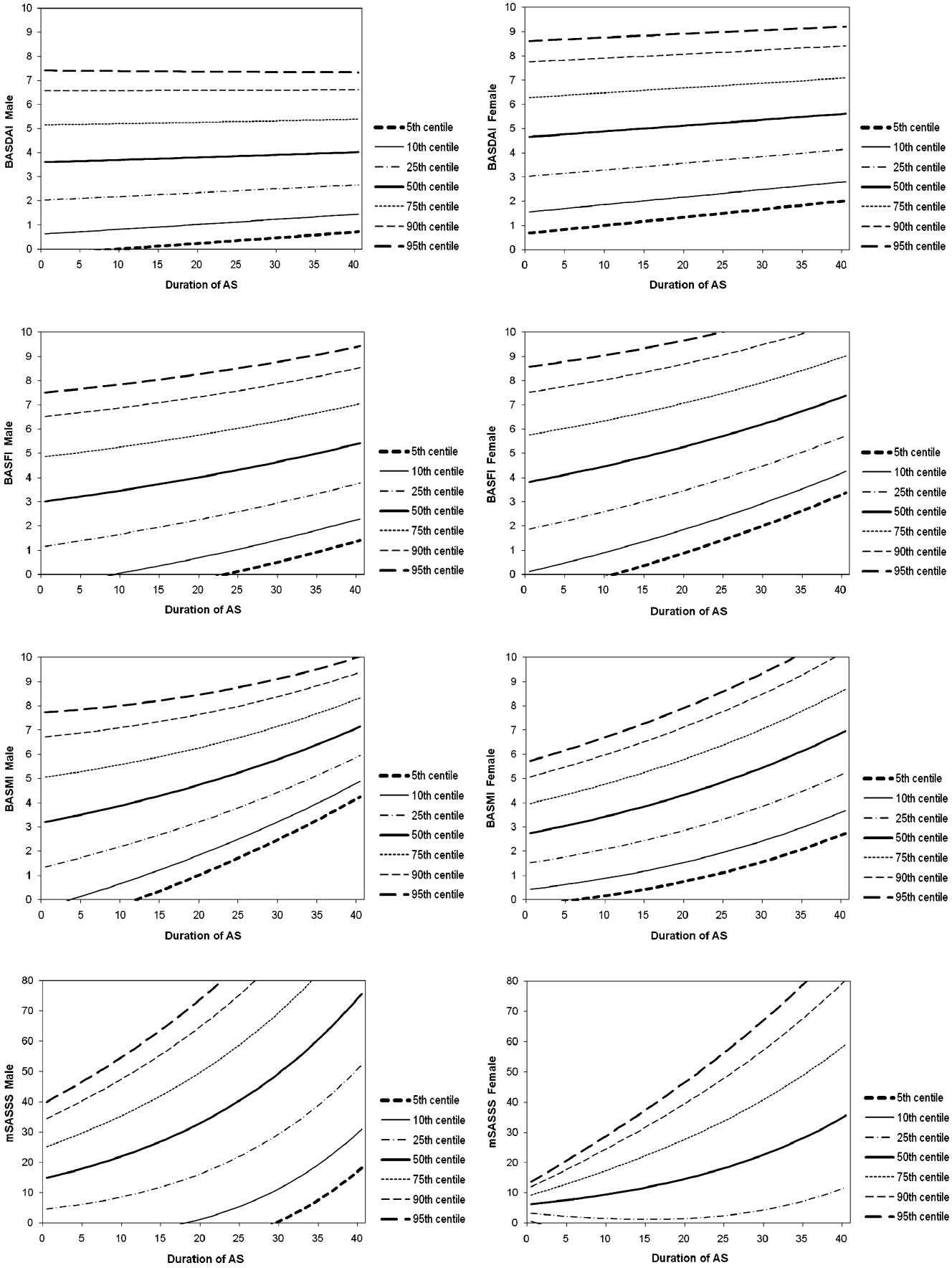
Table 1 summarizes also data about disease activity and its functional and structural repercussion. The patient and physician global assessment (4.7 vs 2.6, $p<0.001$) differed significantly, with physicians scoring disease severity lower than patients. The mean value for BASDAI was 4.2±2.3, for BASFI 4.1±2.7, for BASMI 4.0±2.5 and for mSASSS 20.9±23.1 (obtained from a sub-group of 213 patients that had a complete radiological evaluation, including total cervical and lumbar x-rays). Compared with men, the mean BASDAI in women was 1.2 points higher (4.9 vs 3.7, $p<0.001$) and the mean BASFI was 0.7 points higher ($p=0.010$), but the mean BASMI was 0.8 points lower ($p=0.006$) and the mean mSASSS was 17.6 points lower ($p<0.001$). Comparing the 51 (13.8%) of patients diagnosed with less than 1 year of diagnosis delay with the 86 (23.3%) diagnosed with more than 10 years of diagnosis delay, no significant differences were noted in disease duration adjusted scores (data not shown).

In the overall cohort the mean ESR was 21.7±17.7 mm/h. Regarding HLA B27, 290 of 360 (80.5%) were positive.

The spectrum of the different treatments that patients received at the time of inclusion visit were also depicted. The majority of AS cases were taking NSAIDs (79.1%), and corticosteroids were being used by 17.6% of cases. DMARD were being used by 48.5% of the patients; of these cases 40.8% had only axial involvement. Sulphasalazine in monotherapy was taken by 30.9% of the patients, methotrexate in monotherapy by 8.4% and 6% were taking both. TNF-blockade was being used by 22% of the patients of whom 40.7% had only axial disease. Multiple linear regression analysis revealed a statistically significant higher [1.5 (95% CI: 0.2; 2.8)] BASMI score in patients taking anti-TNF-α therapy (model not shown) as compared to the remaining patients.

Centile charts were developed from a final study population comprising 326 patients for BASDAI, 323 patients for BASFI, 301 for BASMI and 206 for mSASSS. Centile charts were constructed for both genders, showing the 5th, 10th, 25th, 50th, 75th, 90th and 95th centiles (Fig. 1). Our cross-sectional study shows that BASFI,

Fig. 1 BASDAI, BASFI, BASMI and mSASSS reference centile charts for both genders, showing the 5th, 10th, 25th, 50th, 75th, 90th and 95th centiles


BASDAI Male
BASDAI Female
BASFI Male
BASFI Female
BASMI Male
BASMI Female
mSASSS Male
mSASSS Female
Duration of AS
5th centile
10th centile
25th centile
50th centile
75th centile
90th centile
95th centile

BASMI and mSASSS scores continue to increase as a function of disease duration, even after >20 years, in both males and females. By contrast, disease activity assessed by BASDAI did not change over time.

Comparison of AS between genders

As in other populations, in this study AS affected more frequently males than females. The average age, age at symptom onset and the diagnostic delay were similar in both genders. Females reported greater disease activity (BASDAI) and functional impairment (BASFI) but had better metrology (BASMI) and better radiological evaluation (mSASSS). These differences were valid for the results as a whole but also when different periods of disease duration were evaluated.

Discussion

We report here the first characterization of a Portuguese cohort of AS patients. This study describes the socio-demographic, clinical, radiological and biological profile of AS in our country. Furthermore, we have developed reference centile charts for indices of disease activity, function, metrology and mSASSS in our population. This study involved patients recruited from hospital outpatient clinics, a patient population likely to have more severe disease than the overall AS population. Therefore, our centile charts will need to be assessed in a community-recruited AS case cohort before they can be used in non-hospital based settings.

This study confirms that AS in Portugal have similar characteristics to the disease pattern described in other European populations. There is a striking male predominance (62.3% males vs 37.1% females), and the age at symptom onset (26.5±10.8 years) and the frequency of extra-articular features were similar to those reported in previous Portuguese studies [11, 12] or in other studies of white European ethnic groups [13, 14].

Diagnostic delay in this cohort was similar to that reported in other developed countries (7.6±9.0 years) [13–19]. An early diagnosis (less than 1 year after starting symptoms) was established in only 13.8% of the cases. There are many potential explanations for this, but one of the contributors is likely to be the low sensitivity of the New York classification criteria when used in the clinical practice. It will be interesting to observe whether diagnostic delay is reduced with the daily use of the Assessment of SpondyloArthritis international Society (ASAS) undifferentiated spondylarthritis criteria [20]. Interestingly, no statistical difference was found between patients with an early and late diagnosis regarding disease activity, function, metrology and radiological repercussion. This observational data suggests that early diagnosis may not confer a better prognosis. These results must be interpreted in the light of the cross-sectional, observational study design. It may be that early diagnosis is associated with more active disease, reducing the potential benefit of an early intervention rather than simply reflecting paucity of benefit of early treatment. On the other hand, many patients in this cohort were diagnosed as AS cases more than 10 years ago, when therapeutic strategies were clearly different from the ones that are available now.

In terms of therapeutic approach there are some interesting data for analysis. As usual a great proportion of patients are taking NSAIDs (79.1% daily or on demand). A lower but significant proportion of cases (17.6% in total and 12.5% in axial form) are taking corticosteroids. These results reinforce previous results from a preliminary study in Portuguese SPA [11] where corticosteroid prescription was considered higher than in other countries. Sulphasalazine is the most used DMARD (36.9%). TNF-α blockade (22%) is prescribed in a relatively small group of patients as in other studied populations [14, 21] and is used much less often than the estimated proportion of cases thought by expert opinion to warrant treatment with this specific therapy (30–49%) [22, 23]. The positive correlation between BASMI and anti-TNF-α therapy (p=0.024) may be an indirect evidence of the delay in starting biologic therapies in this cohort.

The mean BASDAI (4.2±2.3), BASFI (4.1±2.7) and BASMI (4.0±2.5) values were similar to values of other published cohorts [13, 21, 24].

Reference centile charts have been developed in British AS patients for BASDAI, BASFI and BASMI [8], but no published charts are available from any other population. Furthermore, there is little data about inter-ethnic differences in AS characteristics, and no reference centile charts have been published for mSASSS in any studied population. In constructing centile charts we tried different generalized linear models and selected the generalized linear model with Gaussian family distribution and identity link function (this is linear regression model) for the Bath AS indices and selected the generalized linear model with Gamma family distribution and log link function for mSASSS. In spite of using different statistical methodologies, the smaller sample size available to us and the differences in gender distribution between the two studies, our findings are very similar to those reported previously for the British population [8].

The charts do provide some descriptive information regarding disease activity, functional impairment, metrology and radiological impact in AS over time. These reference charts (Fig. 1), after proper validation, may be applied to compare the same population over time or

different populations. This visual representation may also improve patient understanding of the disease, which may improve patient compliance to treatment. Other potential benefits as their application on an individual basis would require the collection of longitudinal data and trials to confirm them. A potential weakness of the study is that the data is cross-sectional, and it is not yet known to what extent disease activity measures in individual patients track consistently relative to the overall patient cohort. Thus, longitudinal studies are required to determine if patients with high or low outcome measures at one point in time remain consistently high or low at other time points. The patient selection method is another potential limitation of the study, possibly affecting the extent to which the data reflects cases with AS overall in the general population, which may be milder than the clinical cohort studied here. However, as most AS patients in Portugal receive their care through outpatient clinics such as those studied here and in this study a high proportion of those clinics covering a range of demographic regions were included, we feel that this bias is likely to be minor.

Nonetheless, the analyses of BASDAI charts (Fig. 1) confirm the previous finding that AS remains active throughout the disease course [25]. Furthermore, as previously reported in English patients, women are more functionally impaired than men and have greater disease activity despite better metrology and, in our cohort, less radiological change. These results suggest once again differences between men and women in the AS phenotypic expression.

In conclusion, we have described the clinical profile of AS in Portugal, and simultaneously we have constructed the centile charts for BASDAI, BASFI, BASMI and mSASSS. A potential use of these charts is to show changes in the clinical profile of AS patients in Portugal over time due to either changes in treatment strategies or changes in the disease itself. An additional interest would be to facilitate comparisons between different populations.

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Disclosures None.

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