DR. ROSEMARY J HOLLICK (Orcid ID : 0000-0001-6558-7189)

DR. GARETH T JONES (Orcid ID : 0000-0003-0016-7591)

PROF. GARY J MACFARLANE (Orcid ID : 0000-0003-2322-3314)

DR. OVIDIU ROTARIU (Orcid ID : 0000-0003-2322-3314)

Article type : Original Article

The role of metrology in axSpA: does it provide unique information in assessing patients and predicting outcome? Results from the BSRBR-AS registry

Renke L. Biallas, MSc (1), Linda E. Dean, PhD (1), Lesley Davidson, GradDipPhys, BSc Hons (3), Rosemary Hollick, MBChB, PhD, MD (1), Ejaz Pathan, PhD, MD (2), Lindsay Robertson, PhD, MD (3), Gareth T. Jones, PhD (1), Gary J. Macfarlane, MBChB, PhD, CStat, MD, FFPHM (1), Ovidiu Rotariu, PhD (1)

(1) Epidemiology Group and Aberdeen Centre for Arthritis and Musculoskeletal Health, School of Medicine, Medical Science and Nutrition, University of Aberdeen, United Kingdom
(2) Spondylitis Program, Department of Rheumatology, Toronto Western Hospital, Canada.
(3) Rheumatology Unit, Aberdeen Royal Infirmary, Ashgrove House, Aberdeen, United Kingdom.

Corresponding Author:

Professor Gary J Macfarlane

Epidemiology Group

School of Medicine, Medical Sciences and Nutrition

University of Aberdeen

Foresterhill, Aberdeen

AB25 2ZD

E-mail: g.j.macfarlane@abdn.ac.uk

ABSTRACT

OBJECTIVE To determine amongst patients with axSpA 1) factors associated with decreased spinal mobility and 2) whether poor mobility is a predictor of response to anti-TNFα therapy.

METHODS A prospective UK cohort study of persons meeting ASAS criteria for axial spondyloarthritis. At recruitment, clinical and patient-reported factors independently associated with spinal mobility (measured by BASMI) were determined. Amongst those commencing anti-TNFα therapy, factors which were independent predictors of response was determined using ASAS, quality of life and ASDAS response criteria.

RESULTS 1,960 participants were eligible; 70% male, median age 48 years (inter-quartile range 37,59), median BASMI score 3.6(2.2,5.3). Factors independently associated with poor spinal mobility were: poorer function; meeting x-ray criteria for AS; longer symptom duration; higher levels of inflammation (measured by CRP); older age; male gender; not being currently employed and lower levels of education. For 51% of participants, measured BASMI was within 1 of that estimated. Poorer mobility (higher BASMI)

was an independent predictor of not meeting response criteria for ASAS20 (OR per increasing score 0.80(0.66, 0.98)), ASAS40 (0.69(0.50, 0.95)), quality of life (measured by ASQoL) (β 0.64(0.26, 1.02)), but was not related to meeting ASDAS response criteria.

CONCLUSIONS: BASMI was estimated moderately well by other routinely measured factors in patients with axSpA and was an independent predictor of response to biologic therapy for some, but not all, commonly used measures. Consensus around its role in disease monitoring and clinical decisions, particularly in the likely context of face to face consultations becoming less frequent, remains to be established.

Significance & Innovations

- BASMI could be reasonably well estimated in half of patients.
- BASMI was estimated using a combination of socio-demographic, clinical and biological markers.
- BASMI is an independent predictor of treatment response for measures based on BASDAI and/or quality of life, but not ASDAS.
- It will be important to determine how BASMI should be incorporated into disease monitoring and clinical decision making, particularly in the context of face to face consultations becoming less frequent.

Introduction

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease of the axial skeleton, which is characterised predominantly by low back pain, stiffness, and sacroiliitis (1,2). The disease affects between 0.1% and 1.4% of the population, depending on area of the world (3,4).

The impairment of spinal mobility is considered one of the central outcomes in axSpA and has been included in the core set of domains for the evaluation of patients in clinical practice, as defined by the Assessment of Spondylarthritis international Society (ASAS) (5–7). The Bath Ankylosing Spondylitis Metrology Index (BASMI), an index of spinal mobility; consisting of four spinal (cervical rotation, tragus-to-wall distance, modified Schober's test and lumbar lateral flexion) and one hip mobility measurement (intermalleolar distance), is commonly used in clinic, and has been demonstrated to be valid and reliable (8,9). BASMI is one of the few objective measures of spinal disease progression that does not involve imaging. Since its introduction in 1994 (10), BASMI has been widely used in the research community, being cited in over a thousand scientific papers, especially related to clinical interventions and monitoring disease progression in clinical trials (9). Although the measurements of BASMI are relatively easy to perform (9), they are time consuming and should be conducted in-person by trained health care providers. This is particularly relevant in the current context of a pandemic where there is limited opportunity for face to face consultation and indeed even afterwards it is likely that remote consultations will become more common.

A meta-analysis published in 2016 emphasised that "spinal mobility indices and original Schober test have construct validity for structural damage but do not assess true spinal mobility, nor do they reflect levels of inflammation at either the sacroiliac joints and/or the spine." (9). BASMI score can vary significantly within patients, even within the same day (11,12), hence, the relevance of the BASMI score in the daily clinical practice has been questioned. A web-based survey of patients and rheumatologists in 2018 showed that only 65% of rheumatology services in the UK performed BASMI routinely (13). Based on this body of evidence there is a question as to whether the BASMI should remain part of the standard measures used to evaluate patients.

The aim of this study was to (1) determine the factors associated with decreased spinal mobility (higher BASMI score) and (2) determine whether BASMI is an independent predictor of response to first anti-TNFα therapy.

Methods

The British Society for Rheumatology Biologic Register for Ankylosing Spondylitis (BSRBR-AS) is a prospective UK-wide cohort study of patients who meet ASAS criteria for axSpA (5–7). The study received ethical approval from the National Research Ethics Service (NRES) Committee North East – County Durham and Tees Valley (REC ref 11/NE/0374).

Patients were recruited in 83 secondary care centres across Great Britain between December 2012 and December 2017 and were naïve to biologic therapy on recruitment. Patients meeting the Assessment of SpondyloArthritis international Society (ASAS) imaging criteria for axSpA (7) or the modified New York (mNY) definition of Ankylosing Spondylitis (AS) were eligible (14). From November 2014 those meeting the ASAS clinical criteria were also eligible. Details of the study protocol have previously been published (15). There are two participant sub-cohorts: the 'biologic cohort', comprising those patients commencing their first anti-TNFα therapy (i.e. adalimumab, etanercept, certolizumab pegol) at the time of recruitment and the 'non-biologic cohort', who were continuing on therapies other than biologics. The follow-up of biologic patients included planned assessments at 3, 6 and 12 months.

Data collected at recruitment and follow-up

Clinical data included the BASMI (scored 0 – 10 (least to most severe)) (8,10), body mass index (BMI), inflammatory markers (C-Reactive Protein (CRP)), the presence of extra-spinal manifestations (uveitis, psoriasis, inflammatory bowel disease (IBD), enthesitis, dactylitis), a count of comorbidities (myocardial infarct, angina, heart failure, stroke, hypertension, diabetes, asthma, bronchitis, peptic ulcer, liver and renal disease, tuberculosis, demyelination disorders and cancer). We recorded, at the time of recruitment only, whether participants met x-ray criteria (signs of bilateral sacroiliitis (at least grade 2) or unilateral (at least grade 3)) or MRI criteria (signs of active inflammation suggestive of sacroiliitis). Patient-completed questionnaires were used to record demographic and lifestyle factors (tobacco smoking and alcohol intake) as well as Bath Ankylosing Spondylitis indices for disease activity (BASDAI) (16), function (BASFI) (17) and global assessment (BASG) (18), which were scored in the same way as BASMI. Deprivation quintiles, with reference to either the population of Scotland (19), England (20), or Wales (21), were determined by participants' post-codes. Disease specific and general quality of life (QoL) was measured by ASQoL (scored 0 (best) - 18 (worst)) (22), whilst general health was measured by Short Form 12 (SF-12) (scored 0 (worst) - 100 (best)) (23).

Mental health was assessed by the Hospital Anxiety and Depression Scale (HADS) (0 (best) - 21 (worst)) (24). Pain and somatic symptoms were assessed using the widespread pain index (WPI: 0-19) and

symptom severity scale (SSS: 0-12) of the 2011 "research criteria" for fibromyalgia (25), fatigue with the Chalder Fatigue Scale (CFS, 0-33) (26) and sleep disturbance by the Jenkins Sleep Evaluation Questionnaire (0 – 20) (27), with higher scores on each indicating a worse state. Where required, permissions were obtained for use of patient-reported measures.

Outcomes (in the biologics sub-cohort) were measured at the first contact with the study between 10 weeks and 9 months after commencement of anti-TNF therapy (28). The following response outcomes were considered: ASAS20 and ASAS40 (29,30); a clinically important improvement in the Ankylosing Spondylitis Disease Activity Score (ASDAS) (a decrease of at least 1.1); moving from a (very)/high to moderate or inactive ASDAS disease activity state (score <2.1) (31,32); ASQoL (22).

Statistical Analysis

For assessing the ability of patient-reported and other clinical factors to estimate BASMI, data used were from the time of recruitment. Univariable regression analysis was used to investigate the association between BASMI and other variables of interest, with results given as β coefficients (with 95% confidence intervals (CI)). These are interpreted as the change in BASMI per one-unit change in each variable examined. In order to identify a group of factors independently associated with BASMI, forward stepwise regression was used. Factors associated with BASMI at $p \leq 0.2$ during univariable analysis were offered as candidate variables. Factors entered the model at $p \leq 0.1$ and were removed at $p > 0.15$. Variables for which the number of participants was small ($n < 750$: Polysymptomatic Distress Scale, Somatic Symptoms Scale, Generalised Pain, Fibromyalgia and ESR) were excluded. The performance of the model was assessed by testing whether the estimated BASMI values were within ± 1 of the measured BASMI values. This ± 1 threshold was chosen from a previous study which indicated that a 1-point change in BASMI was considered clinically significant (33).

For assessing factors associated with response to therapy, only patients in the biologic sub-cohort were eligible. BASMI measured at the time of recruitment (prior to therapy commencement), as well as other clinical and patient-reported factors, were assessed in terms of their relationship with outcome. Separate models were run for each outcome considered. Univariable regression analysis used logistic regression, except for ASQoL where linear regression was used. Factors associated at a significance threshold of $p \leq 0.2$ (including BASMI) were offered to backward stepwise regression models to determine a parsimonious group of factors that best predict response. Variables were excluded at $p \geq 0.15$ and re-entered at $p \leq 0.1$. For models with a binary outcome, effect measures were odds ratios (OR) with 95% CIs (interpreted as

the increase in odds of the outcome per one unit increase in the predictor variable) and for those with linear outcomes, β coefficients are presented (interpreted as the increase in the outcome variable (ASQoL) per unit increase in the predictor variable).

All statistical analysis was undertaken using STATA (StataCorp LP version 15) and the final BSRBR:AS study download (December 2018) was used.

Results

A total of 1960 participants were eligible for the analysis examining the estimation of BASMI. Approximately two-thirds were male (70%), their median age was 48 years (Interquartile range (IQR) 37, 59) and the median symptom duration 16 years (IQR 7, 30) (Table 1). Of those who had been tested, 80% were HLA-B27 positive. Most participants (68%) met the mNY criteria for AS, an additional 29% ASAS non-radiographic imaging criteria for axSpA, while 3% fulfilled only ASAS clinical criteria for axSpA. The median BASMI score was 3.6 (IQR 2.2, 5.3). For BASDAI, BASFI and BASG the median scores were 4.9 (IQR 2.6, 6.8), 4.5 (IQR 2.0, 7.0) and 5.5 (IQR 2.5, 7.5), respectively.

In the univariable analysis all factors assessed, apart from dactylitis, enthesitis and uveitis, were significantly associated with BASMI (Table 2). BASMI score was positively related to all other Bath Indices (BASFI β = 0.39 (0.35, 0.42), BASDAI β= 0.24 (0.20, 0.28), and BASG β=0.23 (0.20, 0.26)). Participants who were currently employed had a significantly lower BASMI (i.e. better spinal mobility) (β = -1.71 (-1.90, -1.53)), than those not employed. MRI criteria (signs of active inflammation suggestive of sacroiliitis) was associated with a lower BASMI score compared with x-ray evidence of sacroiliitis (bilateral grade 2 or unilateral grade 3) (β = -1.62 (-1.88, -1.36)) as was clinical compared with x-ray criteria (β = -1.71 (-2.49, -0.93)). Higher BASMI scores were observed for participants with comorbidities (per additional comorbidity: β = 0.68 (0.57, 0.78)).

Before undertaking the multivariable model, an assessment for collinearity was conducted and revealed a high linear correlation ($r > 0.7$) between BASFI and five other variables: BASDAI, BASG, ASQoL and SF12-PCS. As BASFI showed the strongest association with BASMI during univariable regression analysis (β = 0.39), and is a key target of axSpA management, it was included as a candidate variable for the multivariable model in preference to the other factors (Table 2).

The final multivariable model (n=1035) included four clinical and four demographic/socio-economic factors as independent estimators of BASMI (Table 3). The clinical factors were: BASFI, β = 0.33 (0.30, 0.36); criteria (MRI (v. x-ray as reference), β = -0.78 (-1.05, -0.52); clinical, β = -0.94 (-1.64, -0.24)); symptom duration (years), β = 0.01 (0.002, 0.02)) and CRP, β = 0.01 (-0.002, 0.02)). The demographic/socio-economic factors were: age (years), β = 0.03 (0.02, 0.04); gender (female); β = -0.25 (-0.45, -0.05); current employment, β = -0.23 (-0.45, -0.004); as well as education. The R^2 for the fit of the model was 0.48 and 51% of the estimated BASMI values were within ± 1 of the measured BASMI values (Figure 1). Estimation was better for patients with BASMI in the mid-range with the model underestimating all people with measured BASMI above 7.

A total of 204 participants were eligible for the analysis examining predictors of response to biologic therapy. Their median age was 48 years (IQR 38, 56), 73% were male and the median follow-up duration was 13.9 weeks (IQR 12.6, 16.4). Of those who had been tested, 79% were HLA-B27 positive. Most participants (81%) met the mNY criteria for AS, an additional 17% ASAS imaging criteria, while 2% fulfilled only ASAS clinical criteria for axSpA. At baseline the median BASMI was 4.6 (IQR 3.0, 5.8) and median ASDAS 3.7 (IQR 3.2, 4.5). At follow-up, 51% and 30% of participants met ASAS20 and ASAS40 response criteria respectively. BASMI measured at recruitment was an independent predictor of both ASAS20 and ASAS40 response with effect measures of response per unit increase, of OR 0.80, 95% CI (0.66, 0.98) and OR 0.69, 95% CI (0.50, 0.95) for ASAS20 and ASAS40 respectively (Table 4). Other significant factors included in the models predicting non-response were higher BMI (both models) and smoking, absence of enthesitis and higher levels of anxiety (ASAS40 only). BASMI was also an important predictor of poor QoL (β 0.64 95% CI (0.26, 1.02)) and other predictors were poorer QoL at recruitment, higher levels of deprivation, a higher BMI and tender joint count, as well as higher levels of anxiety. In contrast, BASMI was not retained in the models based on either the change in, or final level of, ASDAS (Table 4). The outcome of clinically important change in ASDAS was dominated by the initial level of ASDAS while prediction of a final low level of ASDAS only had a single significant predictor – low levels of anxiety.

Discussion

Decreased spinal mobility in patients with axSpA is associated with decreased physical function, being older, male gender, longer symptom duration, not in current employment, lower level of education, meeting X-ray criteria for AS, and having a higher CRP. However, the ability to estimate BASMI based on patient characteristics, patient-reported and clinical factors is modest. Further, we have shown that

BASMI is an independent predictor of treatment response when response is defined in terms of ASAS20/40 or quality of life, but not ASDAS.

The BSRBR-AS registry comprises a relatively large cohort of participants compared to other studies assessing BASMI in the scientific literature (34–39). Most patients seen in rheumatology clinics would have been eligible and recruiting centres included teaching and district general hospitals covering wide geographic areas. The presented analysis has certain limitations. The patient reported data and the measurement of BASMI was not at the same time. BASMI was collected during the routine clinical visit while the patient-reported information was provided when completing the postal-delivered questionnaire which would be received around the time of the first expected routine visit after starting anti-TNF therapy. The measurements of BASMI were at a single point of time and will be subject both to short-term variation which occurs in individuals and measurement error. However, these issues would make it more difficult to estimate BASMI and the data would underestimate the performance of a model so to do. Participants in the dataset predominantly fulfilled the mNY criteria with established x-ray changes (68%), thus, the presented model might be different in a cohort with more non-radiographic axSpA participants, as BASMI scores appear to be lower in this population (34). Whenever there is missing data, there is the possibility of selection bias. This is a particular issue when measuring the prevalence of a disease, symptom or other disease attribute. It is less of a concern when we are measuring the relationship between variables; this should still be unbiased unless there is a different relationship between BASMI and other characteristics in people who had BASMI measured compared to those who did not.

The associations identified here account for around 50% of the variance in BASMI (although as noted above that for methodological reasons this is likely to be an underestimate). This could be due to several reasons; the BASMI may capture something that other measurements do not or there might be other measurements which could estimate BASMI better, but the BSRBR-AS did not collect them (such as more detailed information on imaging). Other than having more detailed information available from imaging (rather than just which criteria are met), it is difficult to identify what these missing factors might be, as the data collected within the BSRBR-AS is based on consensus meetings with consultant rheumatologists to reflect routine clinical practice in the UK and was supervised by an international steering committee. While we show a relationship (on univariable analysis) between mental health measures and BASMI, the data presented here do not allow us to draw conclusions on the temporal nature of this relationship. It could be that mental health directly influences BASMI, but more likely that persons with severe disease (reflected in BASMI) are those most likely to develop poor mental health.

The model estimating BASMI did not perform well for persons with high measured BASMI. The estimated score for all persons with a BASMI over 7 was an underestimate, sometimes by a considerable amount. In a supplementary (unplanned) logistic regression we looked at what factors were associated with having a BASMI >7. Longer disease duration, male gender, meeting X-ray criteria, not currently working and higher levels of anxiety were all significantly related but the fit of the model was poor (R^2=0.16) (data not shown). The first three factors directly contribute to disease progression and hence poor mobility, while the remaining two factors are likely (at least in part) a consequence of poor mobility. It would be important to understand better what factors result in persons having very poor spinal mobility.

Several studies have attempted to identify factors associated with the spinal mobility of axSpA patients. Calvo-Gutierrez, et al. (2015) (37) in a study of 50 patients found that the UCOASMI (University of Cordoba Ankylosing Spondylitis Metrological Index) was independently predicted by structural damage, higher disease activity, older age and longer symptom duration. This is similar to the findings from the current study. Another small study (n=81) based on data collected prospectively in Turkey, also found an independent association between BASMI and older age (years) (β = 0.4), male gender (β = 0.2), HLA-B27 positivity (β = - 0.2) and longer disease duration (years) (β = 0.3) (38). A longitudinal mixed model (39), based on the German Spondyloarthritis Inception Cohort data (n = 210), found an independent association between BASMI and the sacroiliitis sum score (β= 0.12 (95%CI 0.03, 0.21), which is in line with our finding that X-ray evidence of sacroiliitis is associated with poorer spinal mobility.

There are only a few studies examining whether BASMI is a predictor of treatment response; in a study of 624 participants with axial SpA in Switzerland who were starting TNFi therapy, high BASMI was a significant predictor of a not satisfying ASAS40 response criteria at one year follow-up (OR 0.76 per unit increase, 95% CI 0.63, 0.90) (40). BASMI score on commencing TNFi therapy was a predictor of better physical function and spinal mobility at three-year follow-up in a study of 257 AS patients from The Netherlands (41), however BASMI was not an independent predictor of inactive disease (defined by ASDAS<1.3) in a study of 117 AS patients treated with TNFi in Brazil (42). All these results are in agreement with those from the current study. Other prospective studies of treatment response have not considered or included BASMI as a potential predictor (43).

In a five-year prospective study of 166 axSpA patients in Sweden, high BASMI predicted radiographic progression, although only in women (44). In a recent meta-analysis examining factors associated with high IL-23 levels in axSpA patients, including 10 studies with 1724 patients, BASMI was one of two factors along with inflammatory markers (ESR and CRP) to be positively associated (correlation co-efficient 0.46, 95% CI (0.03,0.75)) (45), while a small study of 32 patients with AS in Brazil demonstrated a significant

correlation with IL-6 (46). Mewes et al (2019) in a small study of 55 patients with axSpA showed a strong association between a high BASMI score and poor balance, which in turn was linked to a higher risk of falls (47).

The current study identified that BASMI was reasonably well estimated by other patient-reported and routinely available clinical data. However high measured BASMI scores in particular were not well estimated. Clinical assessments are time consuming and need trained staff (9), although the results from this study show that amongst persons commencing biologic therapy, BASMI was an independent predictor of response for some but not all recognised response criteria. BASMI does not routinely feature in evidence-based guidelines for management of axSpA. For example, the NICE treatment recommendation (48) makes no mention of BASMI or spinal mobility while the ASAS-EULAR recommendations mentions "spinal mobility" as one aspect of the disease for monitoring (49). However, ASAS positively recommends a set of measurements which overlap with but are not identical to the BASMI (50). We also noted in our current study that some centres (27%) did not routinely measure BASMI. This suggests, while the measurement of spinal mobility provides additional information on disease status and for some measures of treatment response, it remains to be determined how this should be incorporated into disease monitoring and clinical decision making, particularly in circumstances where face to face consultations are likely to become less frequent.

Acknowledgements We are grateful to the staff who contributed to running the BSRBR-AS register and to the recruiting staff at the clinical centres, details of which are available at: www.abdn.ac.uk/bsrbr-as

Funding The BSRBR-AS is funded by the British Society for Rheumatology who have received funding for this from Pfizer, AbbVie and UCB. These companies receive advance copies of manuscripts for comments.

Contributors All authors discussed and contributed to designing this study. OR, LED, GJM, and RLB designed the analysis plan, which was undertaken by RLB and overseen by OR, LED and GJM. Results were reviewed by all authors. RLB, OR, GJM and LED all contributed to drafting the manuscript which was critically reviewed by all authors.

Disclaimer Pfizer, AbbVie and UCB have no input in determining the topics for analysis or work involved in undertaking it.

Disclosures The authors have no disclosures in relation to this work.

Competing interests None declared.

Patient consent N/A.

Ethics approval The study was approved by the National Research Ethics Service Committee North East-County Durham and Tees Valley (Research Ethics Committee reference 11/NE/0374).

References

1. van der Linden S, van der Heijde D. Ankylosing spondylitis. Rheum Dis Clin North Am 1998;24:663–76.
2. Dean LE, Macfarlane GJ, Jones GT. Five Potentially Modifiable Factors Predict Poor Quality of Life in Ankylosing Spondylitis: Results from the Scotland Registry for Ankylosing Spondylitis. J Rheumatol 2018;45:62–9.
3. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford) 2014;53:650–7.
4. Sieper J, Poddubnyy D. Axial spondyloarthritis. The Lancet 2017;390:73–84.
5. van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in Ankylosing Spondylitis. J Rheumatol 1999;26:951–4.
6. Zochling J, Braun J. Assessments in ankylosing spondylitis. Best Pract Res Clin Rheumatol 2007;21:699–712.
7. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl 2:ii1–44.
8. van der Heijde D, Landewé R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. Ann Rheum Dis 2008;67:489–93.
9. Castro MP, Stebbings SM, Milosavljevic S, Bussey MD. Construct validity of clinical spinal mobility tests in ankylosing spondylitis: a systematic review and meta-analysis. Clin Rheumatol 2016;35:1777–87.
10. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694–8.
11. de Freitas LV, Rodrigues IK, de Andrade KR, de Castro GRW, Pereira IA, Neves FS. The Bath Ankylosing Spondylitis Metrology Index Varies Significantly During the Daytime. J Clin Rheumatol 2018;24:278–9.

12. Marques ML, Ramiro S, Goupille P, Dougados M, van Gaalen F, van der Heijde D. Measuring spinal mobility in early axial spondyloarthritis: does it matter? Rheumatology (Oxford) 2019;58:1597–1606.

13. Derakhshan MH, Pathak H, Cook D, Dickinson S, Siebert S, Gaffney K. Services for spondyloarthritis: a survey of patients and rheumatologists. Rheumatology (Oxford) 2018;57:987–96.

14. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.

15. Macfarlane GJ, Barnish MS, Jones EA, Kay L, Keat A, Meldrum KT, et al. The British Society for Rheumatology Biologics Registers in Ankylosing Spondylitis (BSRBR-AS) study: Protocol for a prospective cohort study of the long-term safety and quality of life outcomes of biologic treatment. BMC Musculoskelet Disord 2015;16:347.

16. 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.

17. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, 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.

18. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol 1996;35:66–71.

19. The Scottish Government. The Scottish index of multiple deprivation 2016. [Accessed 18 May 2020.] Available from: https://www.gov.scot/publications/scottish-index-multiple-deprivation-2016/.

20. GOV.UK. English indices of deprivation 2015. [Accessed 18 May 2020.] Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015.

21. GOV.WALES. The Welsh Index of Multiple Deprivation 2014. [Accessed 18 May 2020.] Available from: https://gov.wales/welsh-index-multiple-deprivation.

22. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20–6.

23. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–33.

24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

25. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011;38:1113–22.

26. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147–53.

27. Jenkins CD, Stanton B-A, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41:313–21.

28. Macfarlane GJ, Pathan E, Jones GT, Dean ED. Predicting response to anti-TNFa therapy among patients with axial spondyloarthritis (axSpA): results from BSRBR-AS. Rheumatology 2020;0:1–10.

29. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876–86.

30. Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. Ann Rheum Dis 2004;63:1438–44.

31. Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.

32. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cutoff values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47–53.

33. Martindale JH, Sutton C, Goodacre L. An exploration of the inter- and intra-rater reliability of the Bath Ankylosing Spondylitis Metrology Index. Clin Rheumatol 2012; 31:1627–31.

34. Hong C, Kwan YH, Leung Y-Y, Lui NL, Fong W. Comparison of ankylosing spondylitis and non-radiographic axial spondyloarthritis in a multi-ethnic Asian population of Singapore. Int J Rheum Dis 2019;22:1506–11.

35. Chilton-Mitchell L, Martindale J, Hart A, Goodacre L. Normative values for the Bath Ankylosing Spondylitis Metrology Index in a UK population. Rheumatology (Oxford) 2013;52:2086–90.

36. Machado P, Landewé R, Braun J, Hermann K-GA, Baker D, van der Heijde D. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 2010;69:1465–70.

37. Calvo-Gutierrez J, Garrido-Castro JL, Gil-Cabezas J, Gonzalez-Navas C, Ugalde PF, Carmona L, et al. Is spinal mobility in patients with spondylitis determined by age, structural damage, and inflammation? Arthritis Care Res (Hoboken) 2015;67:74–9.

38. Inal EE, Eroglu P, Sunar I, Canak S, Saratas S, Yener M, et al. The parameters affecting the functional and clinical status in patients with ankylosing spondylitis. Medica Mediterranea 2014;30:1403.

39. Protopopov M, Sieper J, Haibel H, Listing J, Rudwaleit M, Poddubnyy D. Relevance of structural damage in the sacroiliac joints for the functional status and spinal mobility in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Res Ther 2017;19:240.

40. Micheroli R, Hebeisen M, Wildi LM, Exer P, Tamborrini G, Bernhard J, et al. Impact of obesity on the response to tumor necrosis factor inhibitors in axial spondyloarthritis. Arthritis Res Ther. 2017;19:164.

41. van Weely SFE, Kneepkens EL, Nurmohamed MT, Dekker J, van der Horst-Bruinsma IE. Continuous Improvement of Physical Functioning in Ankylosing Spondylitis Patients by Tumor Necrosis Factor Inhibitors: Three-Year Followup and Predictors. Arthritis Care Res (Hoboken) 2016;68:1522–9.

42. Shimabuco AY, Gonçalves CR, Moraes JCB, Waisberg MG, Ribeiro ACdM, Sampaio-Barros PD, et al. Factors associated with ASDAS remission in a long-term study of ankylosing spondylitis patients under tumor necrosis factor inhibitors. Adv Rheumatol. 2018;58:40.

43. Arends S, Brouwer E, van der Veer E, Groen H, Leijsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther. 2011;13:R94.

44. Deminger A, Klingberg E, Geijer M, Göthlin J, Hedberg M, Rehnberg E, et al. A five-year prospective study of spinal radiographic progression and its predictors in men and women with ankylosing spondylitis. Arthritis Res Ther. 2018;20:162.

45. Lee YH, Song GG. Circulating interleukin-23 levels in ankylosing spondylitis and their correlation with disease activity: A meta-analysis. Z Rheumatol. 2020 Apr 26. English. doi: 10.1007/s00393-020-00804-4. Epub ahead of print.

46. Rabelo CF, Baptista TSA, Petersen LE, Bauer ME, Keiserman MW, Staub HL. Serum IL-6 correlates with axial mobility index (Bath Ankylosing Spondylitis Metrology Index) in Brazilian patients with ankylosing spondylitis. Open Access Rheumatol. 2018;10:21–25.

47. Mewes KB, Longo B, Campos APB, Simioni J, Skare TL. Balance and falls in axial Spondyloarthritis: a cross sectional study. Acta Reumatol Port. 2019;44:248–253.

48. National Institute for Health and Care Excellence (NICE). Managing spondyloarthritis in adults. [Accessed 13 Jan 2020.] Available from: https://pathways.nice.org.uk/pathways/spondyloarthritis#path=view%3A/pathways/spondyloarthritis/managing-spondyloarthritis-in-adults.xml&content=view-index.

49. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.

50. Landewé R, van Tubergen A. Clinical Tools to Assess and Monitor Spondyloarthritis. Curr Rheumatol Rep. 2015;17:47.

Table 1. Characteristics of the BSRBR-AS patients with measured BASMI

Variable		N	% or Median (IQR)*
Spinal Mobility	BASMI: 0 (best) – 10 (worst)	1960	3.6 (2.2, 5.3)
Demographic factors			
Age	Years	1960	47.8 (36.6, 59.0)
Gender	Male	1375	70.2
	Female	585	29.8
Education	Secondary school	520	33.1
	Apprenticeship	154	9.8
	Further education college	487	31.0
	University degree	302	19.2
	Further degree	109	6.9
Currently employed	No	586	37.0
	Yes	988	63.0
Deprivation,	1. most deprived	393	20.1
quintiles of general population	2	444	22.7
	3	409	20.9
	4	371	19.0
	5. least deprived	340	17.4
Smoking status	Never	670	43.0
	Ex	571	36.7
	Current	316	20.3
Smoking quantity	Low	103	34.4
	Moderate	123	41.1
	High	73	24.4
Alcohol consumption	Never	112	7.2
	Ex	272	17.4
	Current	1175	75.4
Patient reported factors			
Disease Activity	BASDAI: 0 (best) – 10 (worst)	1560	4.9 (2.6, 6.8)
Physical Function	BASFI: 0 (best) – 10 (worst)	1574	4.5 (2.0, 7.0)
Global Health	BASG: 0 (best) – 10 (worst)	1563	5.5 (2.5, 7.5)

Quality of Life	ASQoL: 0 (best) – 18 (worst)	1561	9 (3, 14)
SF-12 – MCS	0 (worst) – 100 (best)	1536	47.1 (37.5, 55.3)
SF-12 – PCS	0 (worst) – 100 (best)	1536	39.2 (29.8, 48.5)
Chalder Fatigue	0 (best) – 33 (worst)	1579	14 (11, 19)
Jenkins Sleep Evaluation	0 (best) – 20 (worst)	1571	10 (5, 15)
Widespread Pain Index	0 (best) – 19 (worst)	751	4 (2, 7)
Somatic Symptoms Scale	0 (best) – 32 (worst)	582	5 (3, 8)
Polysymptomatic Distress Scale	0 (best) – 31 (worst)	582	10 (7, 14)
Generalised Pain	No	453	68.9
	Yes	204	31.1
Fibromyalgia	No	477	73.0
	Yes	176	27.0
Depression	HADS: 0 (best) – 21 (worst)	1561	5 (2, 9)
Anxiety	HADS: 0 (best) – 21 (worst)	1561	7 (4, 11)
Clinical factors			
Symptom duration	Years	1960	16.0 (7.0, 29.5)
axSpA classification	Modified New York	1337	68.2
	ASAS imaging (not mNY)	558	28.5
	ASAS clinical	65	3.3
HLA-B27	Positive	999	51.0
	Negative	252	12.9
	Unknown	709	36.2
Criteria	X-Ray	1382	83.4
	MRI	251	15.1
	Clinical	24	1.5
Comorbidity Count	Range: 0 - 5	1950	0 (0, 1)
Uveitis	No	1461	74.9
	Yes	489	25.1
Inflammatory Bowel Disease	No	1755	90.0
	Yes	195	10.0
Psoriasis	No	1738	89.1

	Yes	212	10.9
Dactylitis	No	1858	95.3
	Yes	92	4.7
Enthesitis	No	1740	89.2
	Yes	210	10.8
Body Mass Index	kg/m^2	1716	27.1 (24.1, 30.8)
C-reactive Protein	mg/dL	1544	0.6 (0.2, 2.0)
ESR	mm	745	11 (5, 23)

*% given for discrete variables, median (IQR) for continuous variables.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASG, Bath Ankylosing Spondylitis Global score; SF-12 – MCS, Mental Component of the Short-Form 12 Health Survey; SF-12 – PCS, Physical Component of the Short-Form 12 Health Survey; CRP, C – reactive protein; HADS, Hospital Anxiety and Depression Scale; Jenkins, Jenkins scale for sleep disturbance.

Table 2. Univariate linear analysis showing association between BASMI and other factors

Variable	Number		Regression coefficient β (95% CI)
Demographic factors			
Age*	1960	Per year	0.06 (0.05, 0.07)
Gender*	1960	Female vs male	-0.58 (-0.78, -0.39)
Education*	1572	Secondary school	Ref.
		Apprenticeship	-0.23 (-0.57, 0.11)
		Further education college	-0.71 (-0.95, -0.48)
		University degree	-1.32 (-1.59, -1.05)
		Further degree	-1.27 (-1.66, -0.87)
Currently employed*	1574	Yes vs no	-1.71 (-1.90, -1.53)
Deprivation*	1957	Per increasing category	0.09 (0.02, 0.16)
Smoking status*	1557	Ex vs never	0.61 (0.39, 0.83)
		Current vs never	0.75 (0.47, 1.00)
Alcohol consumption*	1559	Ex vs never	-0.01 (-0.44, 0.42)
		Current vs never	-0.84 (-1.21, -0.46)
Patient reported factors			
Disease Activity (BASDAI)*	1560	Per unit increase	0.24 (0.20, 0.28)
Physical Function (BASFI) *	1574	Per unit increase	0.39 (0.35, 0.42)
Global Health (BASG)*	1563	Per unit increase	0.23 (0.20, 0.26)
Quality of Life (ASQoL)*	1561	Per unit increase	0.12 (0.09, 0.13)
SF-12 – MCS*	1536	Per unit increase	-0.01 (-0.02, -0.01)
SF-12 – PCS*	1536	Per unit increase	-0.07 (-0.08, -0.06)
Chalder Fatigue*	1579	Per unit increase	0.04 (0.02, 0.06)
Jenkins Sleep Evaluation*	1571	Per unit increase	0.05 (0.03, 0.06)
Widespread Pain Index*	751	Per unit increase	0.10 (0.06, 0.14)
Somatic Symptoms Scale*	582	Per unit increase	0.08 (0.02, 0.13)
Polysymptomatic Distress Scale *	582	Per unit increase	0.07 (0.05, 0.10)

Generalised Pain*	747	Yes vs no	0.89 (0.57, 1.21)
Fibromyalgia*	653	Yes vs no	0.64 (0.30, 0.98)
Depression*	1561	Per unit increase	0.11 (0.09, 0.13)
Anxiety*	1561	Per unit increase	0.04 (0.02, 0.06)
Clinical factors			
Symptom duration*	1960	Per year	0.05 (0.04, 0.05)
HLA-B27*	1251	Negative vs positive	0.31 (0.04, 0.59)
Criteria*	1657	X-Ray	Ref.
		MRI	-1.62 (-1.88, -1.36)
		Clinical	-1.71 (-2.49, -0.93)
Comorbidity Count*	1950	Per unit increase	0.68 (0.57, 0.78)
Uveitis	1950	Yes vs no	0.06 (-0.14, 0.27)
Inflammatory Bowel Disease*	1950	Yes vs no	0.53 (0.23, 0.83)
Psoriasis*	1950	Yes vs no	0.40 (0.11, 0.64)
Dactylitis	1950	Yes vs no	-0.03 (-0.45, 0.38)
Enthesitis	1950	Yes vs no	0.22 (-0.06, 0.50)
Body Mass Index*	1716	Per unit increase	0.06 (0.03,0.08)
CRP*	1544	Per unit increase	0.01 (0.00, 0.02)
ESR*	745	Per unit increase	0.02 (0.01, 0.03)

* eligible for stepwise model (p<0.2)

ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASG, Bath Ankylosing Spondylitis Global score; SF-12 – MCS, Mental Component of the Short-Form 12 Health Survey; SF-12 – PCS, Physical Component of the Short-Form 12 Health Survey; CRP, C – reactive protein; HADS, Hospital Anxiety and Depression Scale; Jenkins, Jenkins scale for sleep disturbance.

Table 3. Results of the stepwise forward model to estimate BASMI

Variables		**Regression coefficient β (95% CI)**
Physical Function (BASFI)	Per unit increase	0.33 (0.30, 0.36)
Age	Per year	0.03 (0.02, 0.04)
Criteria	X-Ray	Ref.
	MRI	-0.78 (-1.05, -0.52)
	Clinical	-0.94 (-1.64, -0.24)
Symptom duration	Per year	0.01 (0.002, 0.02)
Current employment	Yes vs. no	-0.23 (-0.45, -0.004)
CRP	Per unit increase	0.01 (-0.002, 0.02)
Gender	Male	Ref.
	Female	-0.25 (-0.45, -0.05)
Education	Secondary school	Ref.
	Apprenticeship	-0.13 (-0.45, 0.19)
	Further education college	-0.18 (-0.41, 0.04)
	University degree	-0.33 (-0.59, -0.07)
	Further degree	-0.40 (-0.79, -0.02)
Number of obs.	**R-square**	**Adj. R-square**
1,035	0.4824	0.4764

BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C – reactive protein

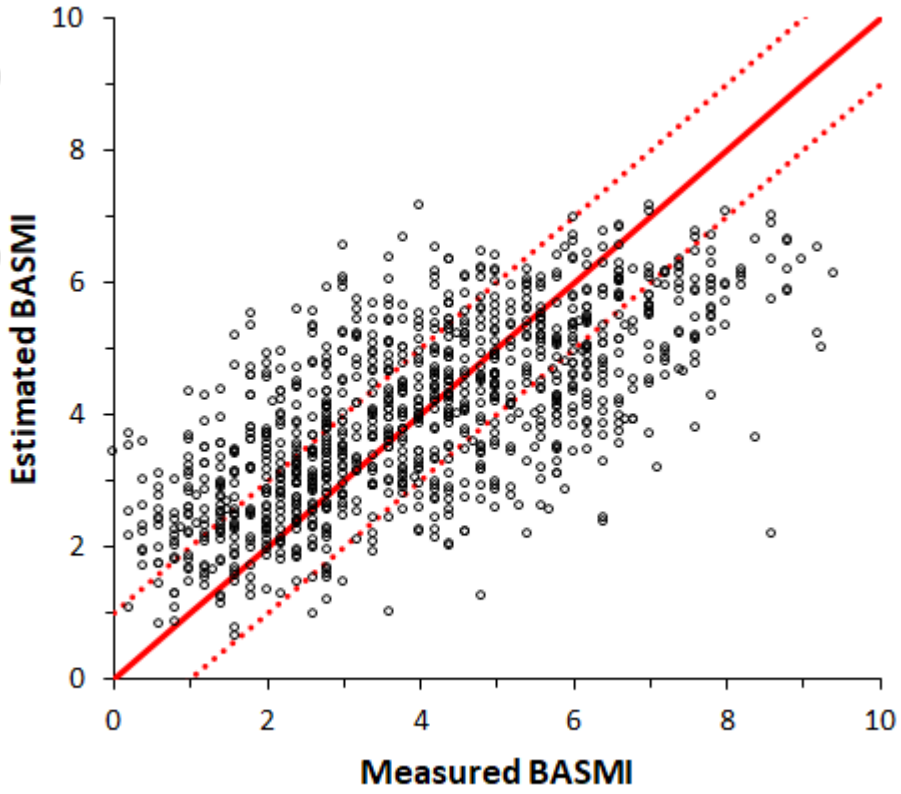

Figure 1. Predictive performance of the final multivariable linear regression model. A hypothetical perfect model would align all points on the 45° continuous red line. The points within the 45° red dotted lines represent predicted BASMI values that were within ± 1 of the measured BASMI.

Table 4. Factors at recruitment associated with response to biologic therapy

Response criteria		**ASAS20**	**ASAS40**	**Δ ASDAS ≥ 1.1**	**ASDAS < 2.1**	**ASQoL***
N participants in model		*N=157*	*N=144*	*N=151*	*N=149*	*N=157*
% meeting criteria		*51%*	*30%*	*47%*	*31%*	*Not applicable*
Variables at recruitment		*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*β (95% CI)*
BASMI	Per unit increase	0.80 (0.66, 0.98)	0.69 (0.50, 0.95)			0.64 (0.26, 1.02)
Age	Per unit increase		0.96 (0.93, 1.003)		0.97 (0.93, 1.004)	
Education	Secondary school				Ref.	
	Apprenticeship				2.72 (0.72, 10.2)	
	College				0.77 (0.25, 2.44)	
	University degree				2.29 (0.81, 6.50)	
	Further degree				3.74 (0.69, 20.6)	
Deprivation	per increasing category				0.77 (0.56, 1.06)	0.60 (0.12, 1.07)
Smoking status	Never		Ref.			
	Ex		0.47 (0.17, 1.29)			
	Current		0.22 (0.06, 0.79)			
Alcohol consumption	Never	Ref.				

	Ex	1.25 (0.27, 5.75)				
	Current	3.02 (0.86, 10.64)				
Body Mass Index	Per unit increase	0.93 (0.87, 0.99)	0.89 (0.81, 0.97)			0.14 (0.02, 0.26)
BASFI	Per unit increase		1.47 (0.99, 2.20)			
Enthesitis	Yes vs no		3.72 (1.03, 13.4)	5.87 (1.28, 26.97)		
SF-12 – MCS	Per unit increase			1.06 (1.01, 1.10)		
SF-12 – PCS	Per unit increase		1.06 (0.99, 1.12)			
ASDAS	Per unit increase	1.28 (0.90, 1.81)	1.90 (0.99, 3.64)	5.25 (2.90, 9.50)	0.77 (0.50, 1.17)	
ASQoL						0.51 (0.33, 0.68)
Comorbidity count	Per unit increase			0.42 (0.24, 0.71)	0.54 (0.29, 1.02)	
Tender joints count				0.83 (0.67, 1.02)		0.19 (0.05, 0.33)
HADS anxiety			0.87 (0.78, 0.97)		0.84 (0.76, 0.94)	0.24 (0.07, 0.41)
CRP			0.94 (0.88, 1.01)			

*ASQoL measured at follow-up

OR, odds ratio; β, linear regression coefficient; Ref, reference category; ASAS, Assessment in Ankylosing Spondylitis; ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; BASMI, Bath Ankylosing Spondylitis Metrology Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; SF-12 – MCS, Short Form 12 Mental Component Score; SF-12 – PCS, Short Form 12 Physical Component Score; HADS, Hospital Anxiety and Depression Scale; CRP, C – reactive protein.