Association between comorbidities and disease activity in axial spondyloarthritis: results from the BSRBR-AS

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Abstract

Objective. Whether comorbidities influence disease activity assessment in axial spondyloarthritis (axSpA) is unclear. Comorbidities inflate DAS28 in rheumatoid arthritis through the patient global score. We examined whether axSpA disease activity measures are differentially affected, and whether comorbidities inflate the AS disease activity score (ASDAS) through the patient global component.

Methods. We used baseline data from the British Society for Rheumatology Biologics Register for AS, including 14 physician diagnosed comorbidities. Linear models were used to compare disease activity (BASDAI, spinal pain, ASDAS, ESR/CRP) according to comorbidity count, adjusted for age, gender, BMI, smoking, socioeconomic status, and education. The same models were used to examine whether patient global was associated with comorbidities, additionally adjusting for other ASDAS components.

Results. 2043 participants were eligible for analysis (67% male, mean age 49 years); 44% had at least one comorbidity. Each additional comorbidity was associated with higher BASDAI by 0.40 units (95%CI 0.27 to 0.52) and spinal pain by 0.53 (95%CI 0.37 to 0.68). Effect size for ASDAS (0.09 units; 95%CI 0.03 to 0.15) was not clinically significant. ESR and CRP were not associated with comorbidity count. Depression, heart failure and peptic ulcer were consistently associated with higher disease activity measures, but not CRP/ESR. Patient global was associated with comorbidity count, but not independently of other ASDAS components (p=0.75).

Conclusion. Comorbidities were associated with higher patient reported disease activity in axSpA. Clinicians should be mindful of the potential impact of comorbidities on patient reported outcome measures and consider additionally collecting ASDAS when comorbidities are present.

Keywords: axial spondylarthritis, ankylosing spondylitis, comorbidity, disease activity, patient global

Key messages:

1. Comorbidity count is associated with significantly higher disease activity measured by BASDAI but not ASDAS.

2. Depression, peptic ulcer and heart failure are associated with higher disease activity, not with CRP/ESR.

3. Comorbidity count does not inflate ASDAS through the patient global score.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease causing pain and functional impairment [1]. Assessing axial disease activity presents unique challenges since the spine and sacroiliac joints – unlike peripheral joints – are not easily accessible for clinical examination. It has been suggested that traditional biomarkers of inflammation – CRP and ESR – do not always reflect the underlying disease activity [2]. Disease activity assessment has traditionally relied on patient-reported outcome measures (PROMs); for example, eligibility to commence and continue biologics are defined using thresholds of BASDAI and spinal pain in the UK [3].

PROMs are important but subjective. Studies have shown that patient perspectives are more closely associated with function and fatigue, whereas physician assessments of disease activity with metrology and CRP [4]. The former may not be specific to axSpA disease activity; for example, cardiorespiratory diseases can significantly reduce function [5,6], while concurrent depression and fibromyalgia will influence fatigue [7].

ASDAS was developed to address some of these concerns [8,9]. ASDAS combines three questions from BASDAI (stiffness, back and peripheral symptoms) with CRP/ESR and the patient global score, analogous to the DAS28 for rheumatoid arthritis (RA). Unlike BASDAI, it has been shown to associate with radiographic progression [10]. However, whether ASDAS is robust to the influence of comorbidities compared to patient-reported disease activity has not been examined. In RA, comorbidity count inflates DAS28 through the patient global score, independently of swollen/tender joints and inflammatory markers [11]. It is unknown whether the same vulnerability exists for ASDAS. Understanding whether and how comorbidities influence assessment of disease activity is crucial given their high prevalent [12,13].

The aims of this study were to 1) compare whether measures of disease activity (BASDAI, spinal pain, ASDAS) and inflammation (CRP/ESR) are differentially influenced by comorbidities, 2) replicate these comparisons for other important measures of disease severity (fatigue, function and quality of life), and 3) examine whether the patient global component of ASDAS is influenced by comorbidities independent of the other components.

Methods

The British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) is a UK-wide prospective cohort study of biologics-naïve patients fulfilling the ASAS criteria for axial SpA. Patients were recruited between December 2012 and December 2017 into two groups: a "biologic" group (those starting biologic DMARDs (bDMARDs)) and a "non-biologic" group (those not). The study protocol [14] and cohort characteristics have been previously published [15]. This analysis focused on baseline (cross-sectional) data before the biologic group started bDMARDs. This analysis used the study dataset of December 2018.

Participating centres obtained physician diagnosed comorbidity data from medical records. The list of comorbidities included: myocardial infarction, angina, heart failure, stroke, hypertension, diabetes, asthma, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, liver disease, renal disease, depression, cancer, tuberculosis (TB) and demyelinating disease. These conditions were selected through a consensus meeting of clinicians and researchers, based on commonly recorded comorbidities in routine practice. Comorbidity status was defined at baseline. Myocardial infarction and angina were combined as ischaemic heart disease (IHD) for this analysis. Extra-articular manifestations of axSpA (uveitis, psoriasis and IBD) were considered disease features rather than comorbidities, given that they share pathogenesis with axSpA and form part of the classification criteria (thereby determining study inclusion) [16,17].

Questionnaires collected PROMs, highest educational attainment, and smoking status. Baseline visits and questionnaires did not necessarily coincide; we included questionnaires within one year before or after the baseline visit for the non-biologic group, and one year before to seven days after for the biologic group (the "eligible window"). Disease activity was assessed using the Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), spinal pain numerical rating scale (NRS); inflammation using CRP (mg/dl) and ESR (mm/hr); functional impairment using Bath AS Functional (BASFI) and Metrology Indices (BASMI); fatigue using the Chalder Fatigue Scale Likert scale (CFQ) which has a range of 0 to 33 with higher scores indicating greater levels of fatigue [18]; and quality of life using the AS quality of life questionnaire (ASQoL) which has a range of 0 to 18 with higher scores indicating poorer quality of life. All patient reported indices were collected at the same time; They are collectively referred to as measures of disease severity throughout the text. To provide context for interpretation of results, minimal clinically important difference in BASDAI is around 1 unit, pain NRS 1.6 units, ASDAS 1.1 units, BASFI 0.6 units, ASQoL (meaningful deterioration) 1 unit, CFQ 2.3-3.3 units, and undefined for the remaining indices [19–23].

ASDAS was calculated using the formula 0.12*Back Pain + 0.06*Duration of Morning Stiffness + 0.07*Peripheral Pain/Swelling + 0.11*Patient Global + 0.58*Ln(CRP+1); that is, questions 2, 3 and 6 from BASDAI, plus patient global which asks "How active was your spondylitis on average during the last week?" [8,9] Where CRP was not available, ASDAS was calculated using ESR [8,9].

Covariates were determined *a priori* based on discussion and causal diagrams [24], including age, gender (female as referent), BMI, smoking status (ever/never), socioeconomic status (as continuous variable) and educational attainment (as dummy variables). Socioeconomic status was approximated using post-code derived Index of Multiple Deprivation (IMD) that related to the specific country of residence within the UK; quintile 1 representing the top 20% most deprived areas and quintile 5 the least deprived [17, 18]. Smoking was categorised as ever and never, since comorbidities will influence smoking cessation behaviour. Similarly, use of NSAIDs in the past 6 months is an intermediate variable, thus excluded as a covariate (see online supplementary materials for causal diagrams and justification).

Ethical approval was obtained from the National Research Ethics Service Committee North East—County Durham and Tees Valley (reference 11/NE/0374) and informed consent was obtained from all participants.

Analysis

Descriptive statistics were used to compare participants with and without comorbidities (t- and Wilcoxon rank-sum tests for continuous variables, Fishers exact test for categorical). The count of 14 comorbidities was entered as a continuous variable into linear models to describe its association with each disease severity measure, adjusting for the above covariates. To test for non-linear relationships and to facilitate interpretation, we also categorised comorbidity count as 0, 1, 2 or ≥3 (only 32 patients (1.6%) had 4 or more comorbidities). CRP and ESR were transformed using ln(CRP+1) and ln(ESR).

We also examined the independent contribution of individual comorbidities to each disease severity measure by adding all 14 comorbidities into linear models, adjusting for the same covariates. Individual conditions may be closely related to others (e.g., hypertension and IHD); we therefore examined variance inflation factors [25] to check for multicollinearity. Correction for multiple testing was not performed since dependent variables all measure the same underlying construct of disease severity.

To examine whether comorbidity count or individual comorbid conditions independently inflated the patient global score, we repeated the above analyses for patient global and comorbidity count or

individual comorbidities, but additionally adjusting for other components of the ASDAS (3 questions and CRP). Throughout, model coefficients and 95% confidence intervals are displayed graphically with detailed results provided in online supplementary materials. Complete case analysis was used throughout with no imputation.

Sensitivity analyses

Some comorbidities, including heart failure, cancer, TB and demyelinating diseases, are routinely sought during the workup for TNF inhibitor therapy. It is therefore possible that these comorbidities are more prevalent in the biologic group due to differential ascertainment alone. We repeated all analyses in only the non-biologic cohort. For analyses of patient global (aim 2), successful adjustment for other components of ASDAS required adequate covariate overlap between comparison groups; extrapolating beyond overlap can introduce bias. We therefore matched patients on all covariates (gender, ever-smoking, education, IMD, quintiles of age and BMI, and tertiles of the three ASDAS questions and ln(CRP+1)) in sensitivity analyses (using coarsened exact matching [26]). All analyses were performed using Stata version 13.

Results

Among a total of 2687 participants, 2043 were included for analysis; exclusions were due to missing questionnaires (n=364), missing comorbidity data (n=6) and questionnaire outside the eligible window (n=274). The analysis population was predominantly male (67%) with mean age of 49.1 years (SD 14.7). Classification criteria for AS was fulfilled by 1316 (65%). HLA-B27 status was available for 74% of participants and was positive in 79% of these cases. The mean BMI was 27.7kg/m^2. Current smoking was reported by 19% of participants, past smoking by 37% and 44% never smoked. 31% were in the biologic group (but not yet commenced on treatment).

The prevalence of each comorbidity is shown in online supplementary figure S1. 44% of participants had at least one of the 14 comorbidities; 27% had 1 comorbidity, 10% had 2, and 5% had 3 or more (online supplementary figure S2).

Table 1 compares participants with and without comorbidities. Those with comorbidities were older, had higher BMI and trend for lower educational attainment. Although there were more ever-smokers in the group with comorbidities (63 v 50%), a larger proportion had quit (43 vs 32%). NSAID use in the preceding 6 months was less common among those with comorbidities. Participants with

comorbidity also had higher disease activity and other measures of disease severity, but similar levels of inflammatory markers.

Table 1. Baseline characteristics compared between participants with and without comorbidities.

		axSpA without comorbidities (n=1127)	axSpA with ≥1 comorbidity (n=886)	p-value
Mean age, years		45.3 (13.5)	53.9 (14.8)	<0.001
Males		742 (66%)	615 (69%)	0.078
Meeting modified New York criteria		703 (62%)	613 (69%)	0.001
Mean age at symptom onset, years		28.4 (11.3)	30.1 (12.3)	0.001
Mean symptom duration, years		16.9 (13.4)	23.8 (15.3)	<0.001
HLA-B27 positive*		702 (80%)	471 (76%)	0.11
Mean BMI, kg/m^2		26.7 (4.9)	28.9 (6.0)	<0.001
Smoking status	Never smoked	563 (50%)	323 (37%)	<0.001
	Ex-smoker	355 (32%)	379 (43%)	
	Current smoker	207 (18%)	181 (20%)	
Education	Secondary school	335 (30%)	308 (35%)	<0.001**
	Apprenticeship	92 (8%)	97 (11%)	
	Further education college	318 (28%)	289 (33%)	
	University degree	275 (25%)	134 (15%)	
	Further degree	102 (9%)	53 (6%)	
NSAID use in past 6 months		865 (77%)	596 (68%)	<0.001
DMARD use in past 6 months		103 (12%)	96 (15%)	0.13
BASDAI, median (IQR)		4.4 (2.3, 6.6)	5.5 (3.3, 7.3)	<0.001
Spinal pain, median (IQR)		3.0 (1.0, 7.0)	5.0 (2.0, 8.0)	<0.001
ASDAS, mean (SD)*		2.2 (1.1)	2.4 (1.1)	<0.001
CRP (mg/dL), median (IQR)*		0.6 (0.2, 1.8)	0.6 (0.2, 2.0)	0.50
ESR (mm/hr), median (IQR)*		10.5 (5.0, 23.0)	11.5 (5.0, 24.0)	0.28
Fatigue, median (IQR)		14.0 (11.0, 18.0)	15.0 (11.0, 20.0)	<0.001
ASQoL, median (IQR)		7.0 (3.0, 12.0)	10.0 (5.0, 15.0)	<0.001
BASFI, median (IQR)		3.6 (1.5, 6.1)	5.7 (2.9, 7.9)	<0.001
BASMI, median (IQR)*		3.2 (2.0, 4.8)	4.4 (2.8, 6.0)	<0.001

Data shown as mean (SD) and n (%) unless otherwise indicated.
*Not all variables had complete data; HLA-B27 was available for 74% of participants, BASMI 75%, ASDAS 78%, CRP 78%, ESR 39%.
**non-parametric test for trend.
IMD, index of multiple deprivation, 1=most deprived, 5=least deprived; IQR, interquartile range; BMI, body mass index; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; BASMI, Metrology Index; ASQoL, AS quality of life questionnaire (range 0-18, higher score indicates poorer quality of life); ASDAS, AS disease activity score; the Chalder Fatigue Scale ranges from 0-33; higher score indicates more fatigue.

Comorbidities and disease activity

With comorbidity count as a continuous variable, each additional comorbidity was associated with higher BASDAI by 0.40 units (95%CI 0.27 to 0.52) and spinal pain by 0.53 (95%CI 0.37 to 0.68). **Figure 1** shows these relationships with comorbidity count as a categorical variable**.** For each additional comorbidity, ASDAS was higher by 0.09 units (95%CI 0.03 to 0.15). Those with 1 or 2 comorbidities did not have higher ASDAS than those with none in terms of statistical or clinical significance. Comorbidity count was not associated with log-transformed CRP (β=-0.03 (back-transformed effect size -0.03mg/dL); 95%CI -0.07 to 0.02) or log-transformed ESR (β=-0.03 (i.e., 0.97mm/hr); 95%CI -0.12 to 0.06).

Independent associations between each comorbid condition and disease activity are shown in **Figure 2**. Participants with depression, heart failure and peptic ulcer diseases had consistently higher disease activity than those without each of these conditions. For example, participants with depression had 0.9-unit higher BASDAI and spinal pain than those without, accounting for covariates and all other comorbidities. Effect sizes were smaller for ASDAS. The only comorbidities associated with CRP and ESR were COPD and asthma, respectively; the back-transformed effect sizes for CRP (0.5mg/dL) and ESR (0.7mm/hr) were not clinically meaningful.

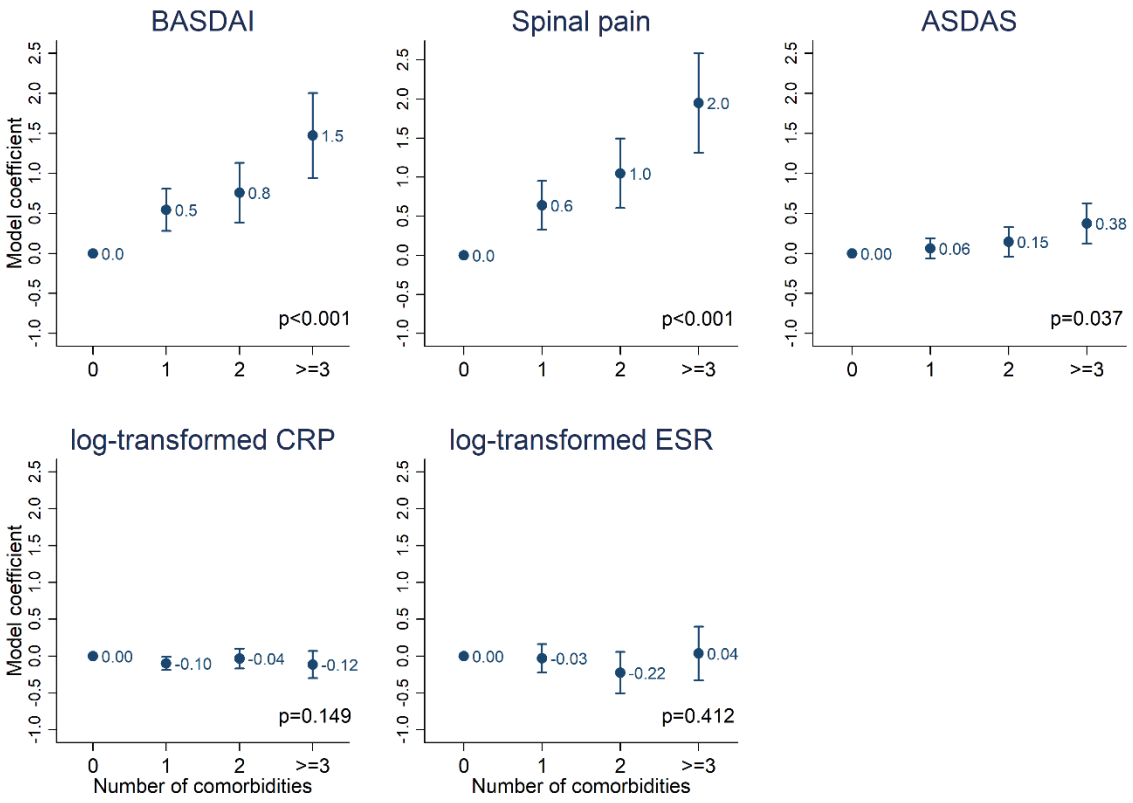

Figure 1. Association between comorbidity count and disease activity. Results shown as adjusted model coefficients with 95% confidence intervals using participants with no comorbidities as the reference group; covariates were age, gender, BMI, smoking status, socioeconomic status and education. For example, participants with ≥3 comorbidities had 1.5-unit higher BASDAI and 0.38-unit higher ASDAS than those without comorbidities.

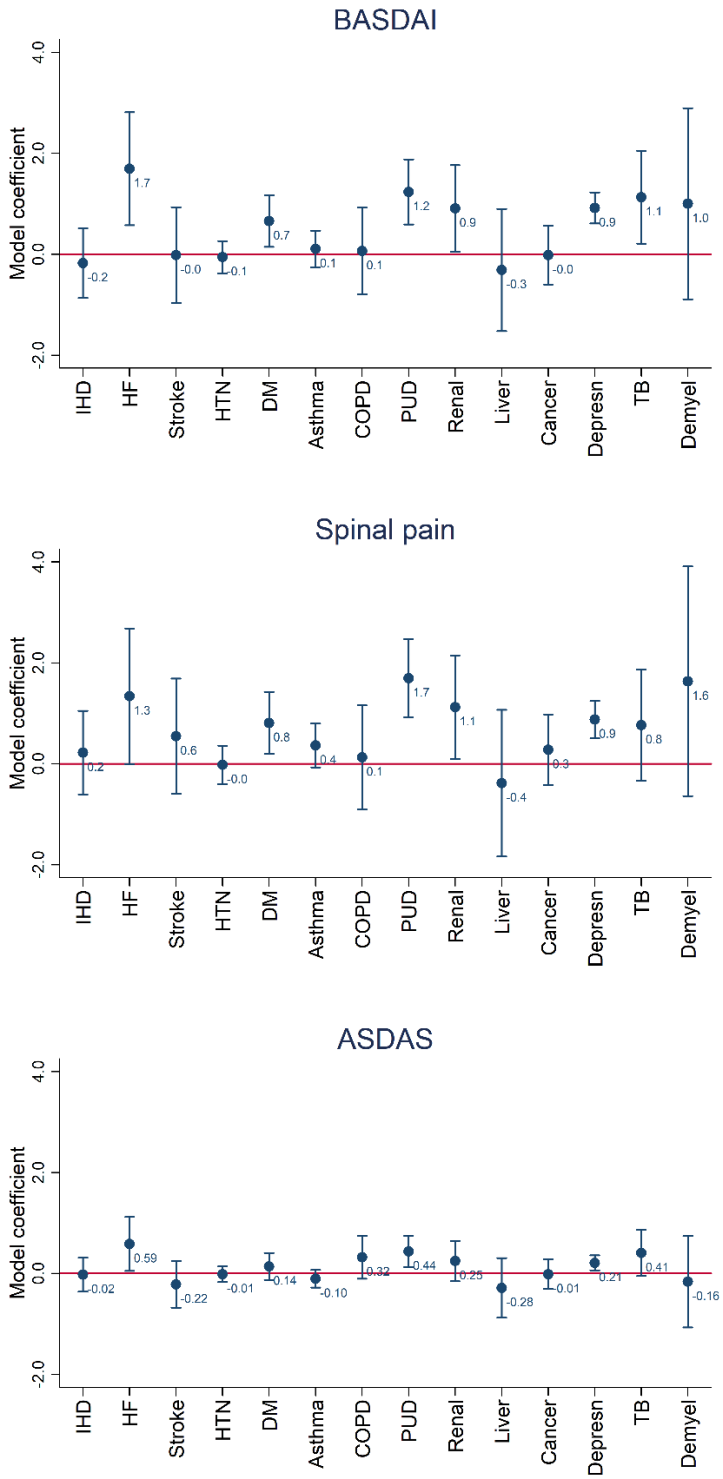

Figure 2. Association between each comorbid condition and disease activity. Results shown as adjusted model coefficients with 95% confidence intervals compared to participants without each condition; covariates were age, gender, BMI, smoking status, socioeconomic status and education. For example, participants with heart failure (HF) had 1.7-unit higher BASDAI and 0.59-unit higher ASDAS than those without HF. IHD, ischaemic heart disease; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PUD, peptic ulcer disease.

Comorbidities and other measures of disease severity

Comorbidity count (as continuous variable) was significantly associated with worse fatigue (β=1.05; 95%CI 0.76 to 1.33), quality of life (β=1.18; 95%CI 0.90 to 1.46) and functional impairment (β=0.55; 95%CI 0.41 to 0.69). Effect size was smaller for BASMI (β=0.22; 95%CI 0.12 to 0.33) than BASFI. **Figure 3** shows these relationships with comorbidity count as a categorical variable.

Independent associations between each comorbid condition and the four disease severity measures are shown in **Figure 4**. Participants with heart failure, depression and peptic ulcer disease had consistently worse fatigue, quality of life and functional impairment than those without, accounting for covariates and all other comorbidities. Diabetics had worse function and quality of life, while participants with stroke had higher fatigue. The only comorbidities associated with CRP and ESR were COPD and asthma, respectively; the back-transformed effect sizes for CRP (0.5mg/dL) and ESR (0.7mm/hr) were not clinically meaningful.

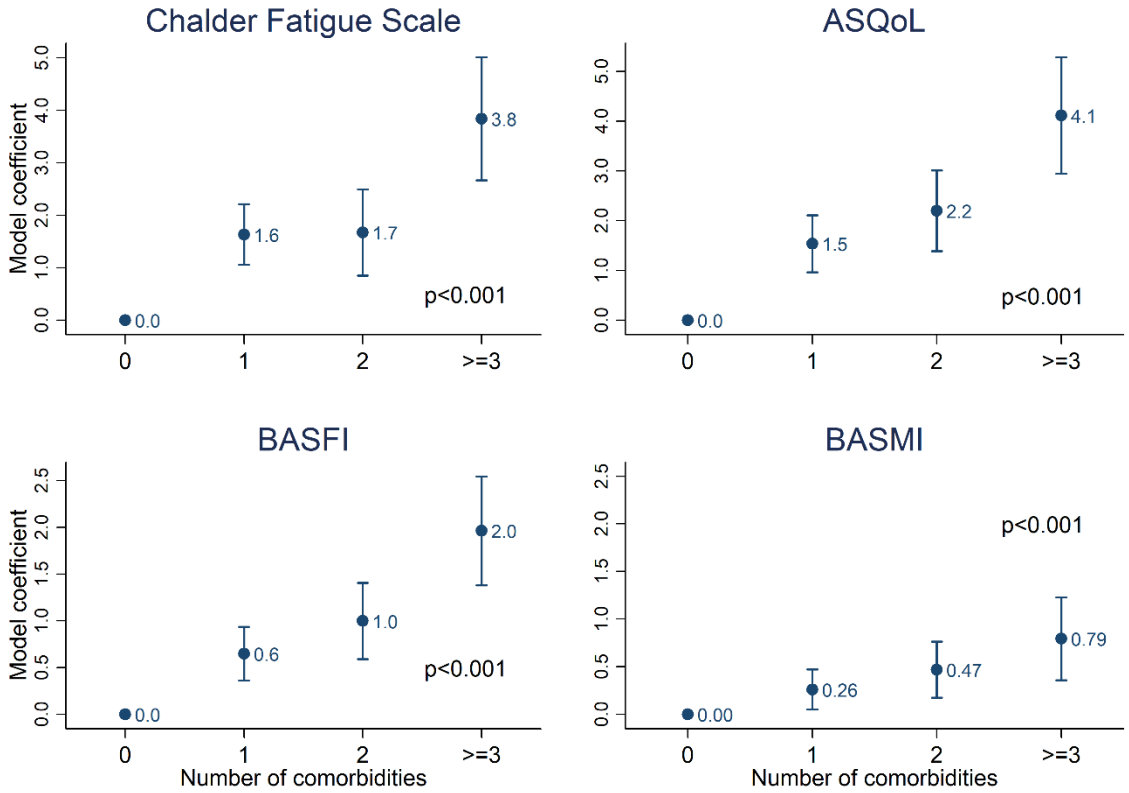

Figure 3. Association between comorbidity count and other measures of disease severity. Results shown as adjusted model coefficients with 95% confidence intervals using participants with no comorbidities as the reference group; covariates were age, gender, BMI, smoking status, socioeconomic status and education. For example, participants with ≥3 comorbidities had 2.0-unit higher BASFI and 0.79-unit higher BASMI than those without. ASQoL, AS quality of life questionnaire.

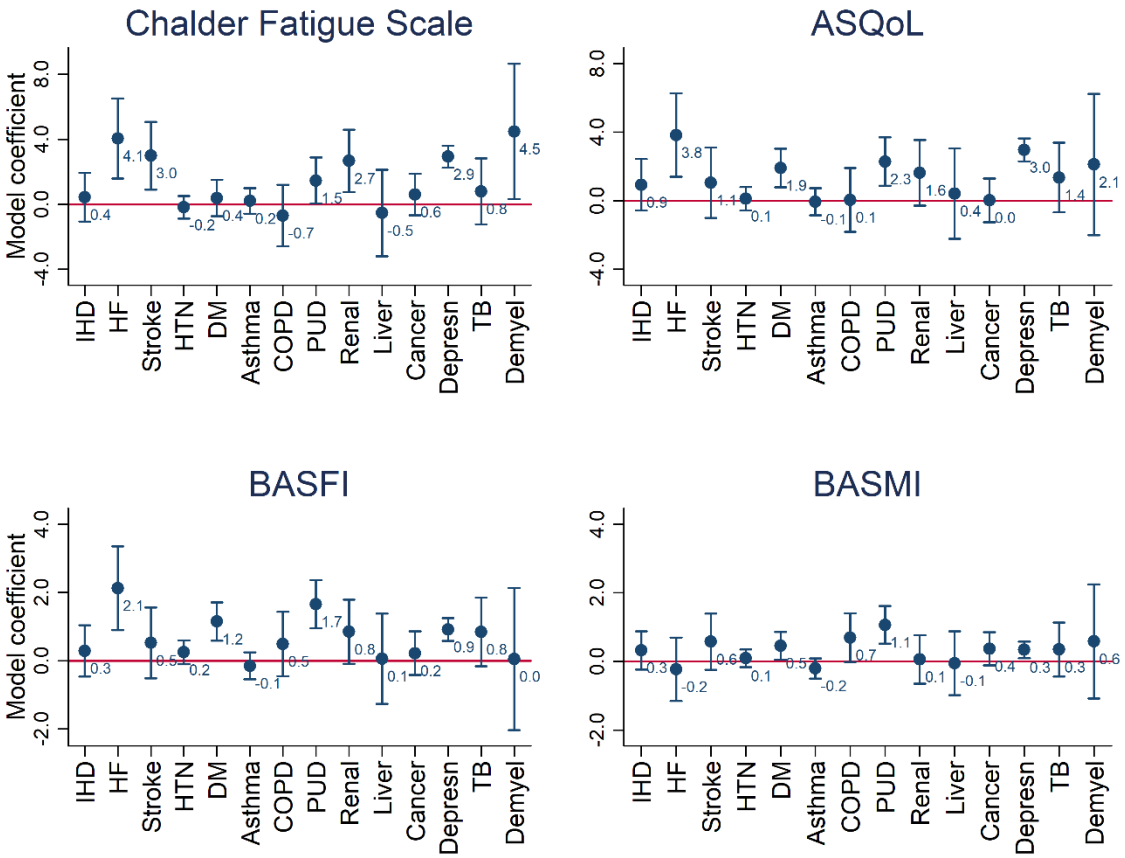

Figure 4. Association between each comorbid condition and other measures of disease severity. Results shown as adjusted model coefficients with 95% confidence intervals compared to participants without each condition; covariates were age, gender, BMI, smoking status, socioeconomic status and education. IHD, ischaemic heart disease; HF, heart failure; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PUD, peptic ulcer disease.

Independent influence of comorbidity on the patient global component of ASDAS

Patient global score increased (suggesting an increase in disease severity) with the number of comorbidities, but not independently of other ASDAS components (**Figure 5**). Depression, peptic ulcer and renal diseases were significantly associated with patient global, but not when additionally adjusting for other ASDAS components.

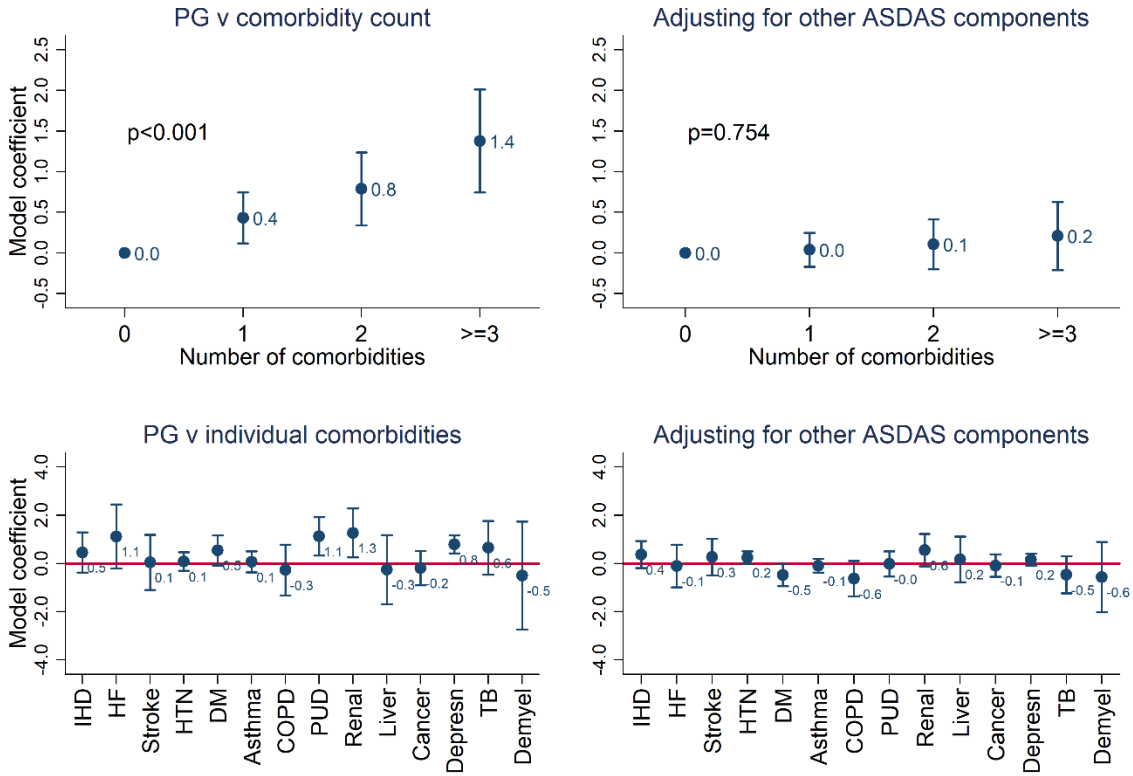

Figure 5. Association between the patient global score and comorbidity. Results shown as model coefficients with 95% confidence intervals; covariates were age, gender, BMI, smoking status, socioeconomic status and education

Results from both sensitivity analyses (see online supplementary materials) did not materially change effect estimates, but precision was reduced (i.e., confidence intervals widened) with smaller sample sizes.

Discussion

Patient-reported axSpA disease activity increased with the number of comorbidities in this cross-sectional study. Unlike BASDAI and spinal pain, ASDAS was not associated with comorbidity count or individual comorbidities at a clinically meaningful effect size. Although patient global score was influenced by coexisting morbidities, they did not inflate ASDAS through the patient global score independently of other ASDAS components. When making treatment decisions, clinicians should be mindful of the potential impact of comorbidities on patient reported measures of disease activity and other measures of disease severity. Disease activity should be assessed using ASDAS when comorbidities are present.

A key strength of this study is its large sample size from a broad range of rheumatology centres, for whom a wide range of disease measures were collected. Ascertainment of comorbidities was robust, using physician diagnoses from medical records. There were also limitations. Selection of comorbidities was not tailored for this secondary analysis; therefore some (e.g., neurological or infectious) comorbidities were not compared. However, included comorbidities were broadly representative of important diseases when compared to prior axSpA research [12]. Low prevalence of some conditions (e.g., heart failure, liver and demyelinating diseases) meant that their effect estimates had significant uncertainty. Severity (e.g., for heart failure) and more granular description (e.g., cancer type) for comorbidities were not available but would have provided useful information. Some comorbidities (TB, heart failure, cancer and demyelinating diseases) are of special interest when considering TNF inhibition therapy; they may be recorded more systematically in patients. However, restricting analyses to the non-biologic cohort did not meaningful change results. Lastly, Wording of the patient global question can be highly variable [27]. For example, the patient global in DAS28 can be worded to assess arthritis-related disease activity or global health (the recommended phrasing in RA is “Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?”). In our data, patient global was specific to spondyloarthritis activity in the past week; therefore, other versions may not be equally robust the presence of comorbidities.

Our results complement those from the ASAS-COMOSPA study, where comorbidity burden (assessed using RDCI) was associated with worse BASFI, quality of life (EuroQol) and work-related outcomes, despite using a slightly different list of comorbid conditions [5]. We additionally demonstrated that BASMI – a physician derived outcome often considered objective – is also significantly associated with comorbidity count, albeit with smaller effect sizes than BASFI. Importantly, we showed ASDAS to be comparatively robust to the presence of coexisting morbidities. Unlike BASDAI and spinal pain, the relationship between comorbidity count and ASDAS was not completely linear, which may be

explained by the weighting of ASDAS components. ASDAS was not significantly different between participants without comorbidities and those with 1 or 2, but the effect size was proportionately larger for ≥3 conditions. Nevertheless, a mean difference of 0.38 between those with ≥3 conditions and none is not clinically significant (meaningful change = 1.1). Our use of an unweighted comorbidity count was preferable, since RCDI was weighted for inpatient outcomes (i.e., mortality, hospitalization, disability, and costs) that may not be appropriate to study axSpA-specific measures. It also allowed us to examine the relationship between comorbidity and outcomes in more detail: depression, diabetes, heart failure, peptic ulcer and renal diseases were the most significant contributing conditions.

Neither the ASAS-COMOSPA nor our cross-sectional study could establish causal relationships. For example, heart failure is likely to cause functional impairment, but participants with heart failure may also have reduced access to treatment (NSAIDs and TNFi) to reduce functional decline. Similarly, renal and peptic ulcer diseases can be contraindications for symptomatic control with NSAIDs, but may also result from long-term need for NSAIDs due to active disease. These are limitations arising from the cross-sectional design and lack of historical NSAID data. Results from our analysis do, however, suggest that outcomes such as ASDAS and BASMI are less influenced by comorbidities than patient-reported measures.

In RA, patient global increased with the number of comorbidities, independently of tender/swollen joint count, CRP and physician global [11]. Among axSpA participants in this study, patient global was significantly associated with comorbidity count, but not independently so when adjusting for other ASDAS components. This further reassures and supports the use of ASDAS, particularly when comorbidities are present and likely to influence other outcome measures. Further longitudinal studies are needed to assess whether comorbidities influence treatment response as measured by different outcomes. Longitudinal studies on comorbidities as “exposure” (rather than outcome) in axSpA are scarce. Preliminary results from the BSRBR-AS suggests that comorbidity may be one of very few potentially modifiable predictors of treatment response [28].

In summary our results suggest that patient-reported axSpA measures are influenced by coexisting morbidities. This is important for routine practice as around half of all patients have at least one comorbidity. ASDAS seems to be less vulnerable to the presence of comorbidities. ASDAS was not disproportionately inflated by the patient global score as was shown for DAS28 in rheumatoid arthritis. In routine clinical practice, clinicians should consider additionally collecting ASDAS to assess disease activity in patients with multiple comorbidities, including but not limited to depression.

Further studies should examine the impact of comorbidity burden on longitudinal disease severity and response to treatment.

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Disclosures: The authors declare no conflicts of interest.

Contribution: SSZ analysed the data and wrote the manuscript, with significant input from all co-authors. GJM and GTJ are Chief Investigator and Deputy Chief Investigator respectively on BSRBR-AS and designed the study and oversaw its conduct. In the current project they discussed results and provided input into drafts of the manuscript.

Data availability: Data from the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis are available to external investigators, on reasonable request. For information on how to access data, see: http://www.rheumatology.org.uk.

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