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Impact of the number of comorbidities on the outcome measures and on the retention rate of the first anti-TNF in patients with Ankylosing Spondylitis. Two-year follow-up in REGISPONSER-AS

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A B S T R A C T

Objectives: To evaluate the impact of the number of comorbidities on the outcome measures after two years of follow-up in patients with Ankylosing Spondylitis (AS) and to determine whether the number of comorbidities influences the retention rate of the first anti-TNF.
Methods: This was an observational and prospective study conducted during 2 years of follow-up in the REGISPONSER-AS registry. The patients were divided into three groups according to the number of comorbidities at baseline (0, 1 or ≥2). Linear regression models adjusted for disease duration, age, sex and smoking were constructed to evaluate the association between the number of comorbidities and the Patient Reported Outcomes (PRO) scores. The impact of the number of comorbidities on PROs over two years of follow-up was evaluated using mixed models for repeated measures adjusted for disease duration, age, sex and smoking. Finally, the retention rate of the first anti-TNF antibody across the three groups was evaluated using a log-rank test.
Results: Patients with two or more comorbidities showed higher scores at baseline and during the two years of follow-up for the Global VAS, BASDAI, ASDAS, and BASFI and worse scores for the physical component of the SF12. A higher probability of discontinuation of the first anti-TNF was found in patients with 2 or more comorbidities compared with the patients in the other groups (38.2% vs. 26.6% vs. 25.4% for ≥2 comorbidities, 0 and 1 comorbidity, respectively), although these differences were not significant (log-rank test: *p*-value = 0.180).
Conclusion: In patients with AS, the presence of 2 or more comorbidities was associated with worse scores on the outcome measures test after two years of follow-up and a greater tendency of discontinuation for the first anti-TNF.

Introduction

Axial spondyloarthritis (axSpA) is an inflammatory disease that predominantly affects the axial skeleton and sacroiliac joints [1]. Based on the presence of radiographic changes of the sacroiliac joints, it is divided into nonradiographic (nr-axSpA) and radiographic axSpA (r-axSpA, i.e., Ankylosing Spondylitis (AS)) [2]. axSpA can be associated with several extra-articular manifestations and comorbidities. We define a comorbidity as the presence of a concomitant medical condition, while extra-articular manifestations refer to non-articular features that share the same etiopathogenesis as axSpA (uveitis, psoriasis, and inflammatory bowel disease) [3].

Comorbidities are more frequent in axSpA patients than in the general population, partly due to the sequelae of systemic inflammation or its treatments [4]. The most frequent comorbidities observed in SpA patients are osteoporosis, cardiovascular disease (CVD), cancer and infections [5]. Comorbidities are essential for the management of patients with axSpA. They influence treatment decisions, and they are associated with worse physical function, quality of life and work-related outcomes [6]. An increased risk of mortality has been described in SpA patients in comparison with the general population, partly explained by the increased risk of CVD in these patients [7].

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The efficacy of tumor necrosis factor alpha inhibitors (anti-TNF) as a treatment in axSpA has been widely demonstrated in randomized controlled trials [8]. However, many of these patients discontinue the treatment due to a lack of efficacy, while remission is rarely the reason for withdrawal. Several studies have searched for predictors of a response and adherence to anti-TNF in patients with axSpA. However, very few studies have evaluated the effect of comorbidities on anti-TNF drug retention. A recent study showed that a history of CVD, chronic lung disease and several socioeconomic factors were associated with an increased risk of discontinuing anti-TNF therapy [9].

Many studies have evaluated the impact of comorbidities on the different outcome measures but have not investigated the impact of such comorbidities over time. Moreover, few studies have evaluated the influence of the number of comorbidities on anti-TNF adherence. In this context, we decided to conduct this study, with the aim of evaluating the impact of the number of comorbidities on the outcome measures after two years of follow-up and evaluating how the number of comorbidities influenced adherence to the first anti-TNF therapy in patients with AS.

Patients and methods

Patients

This is an observational, longitudinal and prospective study including a subgroup of 749 patients (REGISPONSER-AS) from the REGISPONSER study (Spondyloarthritis Registry of the Spanish Rheumatology), which was conducted by GRESSER (Spanish Group for the Study of Spondyloarthritis of the Spanish Rheumatology Society). REGISPONSER is a Spanish registry that incorporated SpA patients who fulfilled European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthritis between March 2004 and March 2007 [10]. This was a multicentre study in which 21 centres participated.

The design, sampling and recruitment of patients in the registry have been previously described [11]. Patients were consecutively included, and each patient was assigned a random code in the database. A randomized sample of patients from the original REGISPONSER registry were included in the REGISPONSER-AS prospective study if they fulfilled the following inclusion criteria: (A) confirmed cases of Ankylosing Spondylitis (AS) as defined by the modified New York criteria [12]; (B) blood tests available within 15 days of the visit and a complete radiographic study within the previous year; and (C) agreement to complete all self-administered questionnaires. The total follow-up period was 5 years, with one visit per year, although in this study, we only considered the first two years of follow-up. A flow-chart showing the causes of exclusion from the study is displayed in Supplementary Fig. 1, and the comparison of baseline clinical characteristics between patients excluded and included in REGISPONSER-AS is shown in Supplementary Table 1.

This study was approved by the Ethics Committee ("Comisión de Ética e Investigación Sanitarias") of the Reina Sofia University Hospital from Córdoba (Spain) on 21 April 2006, and each of the participants signed an informed consent form to participate in the REGISPONSER registry.

Collected variables

A case report form was used to collect the following data:

(A) Sociodemographic data: sex, age, university education, marital status, exercise, and smoking status.

(B) Clinical characteristics and SpA features: age of onset of SpA, disease duration (years between symptom onset and the study visit), diagnostic delay (years between symptom onset and SpA diagnosis), family history of SpA, HLA-B27 antigen status, C-reactive protein (CRP, mg/dL), erythrocyte sedimentation rate (ESR), synovitis, psoriasis, inflammatory bowel disease (IBD), enthesitis, dactylitis, uveitis, swollen joints, painful enthesis according to the Maastricht Ankylosing Spondylitis Score (MASES) [13], hip involvement and hip prosthesis.

(C) Patient-reported outcomes (PROs): the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [14], the patient's global visual analogue scale (global VAS) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) [15] were collected for all patients to assess disease activity. The Bath Ankylosing Spondylitis Functional Index (BASFI) is used to evaluate function in these patients [16]. Structural damage was evaluated using the Bath Ankylosing Spondylitis Radiology Index (BASRI) [17]. The Mental Health Survey (MSF12) and the Physical Health Survey (FSF12) were filled out by the participants [18].

(D) Past and current treatment: Data on previous or concomitant treatments were collected, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs), csDMARDs (sulfasalazine, methotrexate or leflunomide) and bDMARDs (anti-TNF treatment). The dates of bDMARD initiation and withdrawal were collected.

(E) Comorbidities: hypertension, type 1 diabetes mellitus (DM), type 2 DM, hypercholesterolemia, gastrointestinal ulcer, myocardial infarction, angina, congestive heart failure, stroke, peripheral venous disease, chronic obstructive pulmonary disease, cancer, metastasis, dementia, moderate liver disease, infection, acquired immunodeficiency syndrome (AIDS), depression, accidents, cytopenia, chronic kidney failure, amyloidosis, atlantoaxial subluxation, demyelinating disease and other comorbidities. All of these comorbidities were confirmed using the patients' medical records.

Statistical analysis

Descriptive data are shown as the mean and standard deviation (SD) for quantitative variables and as absolute and relative frequencies for qualitative variables.

According to the number of comorbidities at baseline, the patients were divided into three groups: 0, 1 or $\geq$2 comorbidities. Baseline clinical characteristics, disease activity, PROs and treatments were compared across the three groups using chi-squared tests and ANOVA tests for binary and continuous variables, respectively.

To evaluate whether the number of comorbidities influenced the values of the PROs (β coefficient), linear regression models were conducted using the PROs as the dependent variable and the three groups of patients according to their comorbidities as explanatory variables. Since disease duration, age, sex and smoking may influence both the number of comorbidities and the PROs, additional models adjusted for these variables were explored.

After that, the impact of the number of comorbidities on PROs over two years of follow-up was evaluated using mixed models for repeated measures (MMRM), adjusting for disease duration, age, sex and smoking.

Finally, we compared the retention rate of the first anti-TNF across the three groups of patients (i.e., 0, 1 or $\geq$2 comorbidities) using a Kaplan-Meier curve and a log-rank test.

All contrasts were bilateral and considered significant when the p-value < 0.05. Data were collected, processed and analysed using IBM SPSS Statistics v.25 (SPSS, Inc., Chicago, IL) and RStudio 1.4.1106.

Results

A total of 749 patients with a diagnosis of AS were included in the analysis. A total of 352 (47.0%) patients had no comorbidities, 183

Table 1
Baseline characteristics according to the number of comorbidities.

		Number of comorbidities			
	Total N = 749	0 comorbidities N = 352	1 comorbidity N = 183	≥ 2 comorbidities N = 214	p-value*
Sex (male)	564 (75.3%)	250 (71%)	142 (77.6%)	172 (80.4%)	**0.031**[b]
Age, mean (SD)	48.4 (12.2)	43.1 (11.4)	49.2 (10.1)	56.3 (10.6)	**0.000**[a,b,c]
Age of onset, mean (SD)	27 (10.3)	25.1 (8.7)	27.4 (10)	29.9 (12.1)	**0.000**[a,b]
Disease duration, mean (SD)	21.4 (12.7)	18.1 (11.7)	21.9 (11.7)	26.3 (13.6)	**0.000**[a,b,c]
Diagnosis delay, mean (SD)	8 (9.5)	7.4 (8.7)	7.67 (9.1)	9.5 (10.8)	**0.034**[b]
University studies	91 (12.1%)	58 (16.5%)	14 (7.7%)	19 (8.9%)	**0.003**[a,b]
Single	101 (16.3%)	63 (20.3%)	22 (13.2%)	24 (12.7%)	**0.038**[b]
Exercise	314 (41.9%)	164 (46.6%)	71 (38.8%)	79 (36.9%)	0.059
Smoking (ever)	362 (51.9%)	149 (48.4%)	93 (52%)	120 (57.1%)	0.146
Family history of SpA	420 (59.9%)	195 (60.2%)	105 (60%)	120 (59.4%)	0.984
HLA-B27 positive	586 (81.3%)	283 (83%)	140 (79.5%)	163 (79.9%)	0.533
Synovitis	250 (33.4%)	114 (32.4%)	60 (32.8%)	76 (35.7%)	0.708
Psoriasis	76 (10.2%)	36 (10.3%)	17 (9.3%)	23 (10.8%)	0.882
Inflammatory bowel disease	45 (6%)	25 (7.1%)	12 (6.6%)	8 (3.7%)	0.247
Enthesitis	236 (31.9%)	113 (32.4%)	54 (29.8%)	69 (33%)	0.775
Dactylitis	55 (7.4%)	23 (6.6%)	12 (6.6%)	20 (9.4%)	0.402
Uveitis	154 (20.7%)	77 (21.9%)	33 (18.1%)	44 (20.9%)	0.597
Swollen joints, mean (SD)	0.3 (1.6)	0.3 (1)	0.3 (1.8)	0.3 (2)	0.877
Painful enthesis, mean (SD)	2.2 (1.9)	2.3 (1.9)	2.1 (1.8)	2.2 (1.9)	0.849
Hip involvement	183 (24.8%)	71 (20.5%)	48 (26.8%)	64 (30.3%)	**0.025**[b]
Hip prothesis	34 (4.6%)	10 (2.9%)	7 (3.8%)	17 (8%)	**0.017**[b]
NSAIDs	566 (75.9%)	259 (73.8%)	139 (76.4%)	168 (78.9%)	0.386
csDMARDs	155 (20.9%)	72 (20.7%)	43 (23.6%)	40 (18.9%)	0.507
AntiTNF	157 (21%)	70 (19.9%)	45 (24.6%)	42 (19.6%)	0.381
ESR, mean (SD)	18.4 (16)	17.2 (13.7)	18 (16.5)	20.4 (18.7)	0.088
CRP mg/dl, mean (SD)	9.2 (13.2)	8.6 (11.7)	8.5 (11.3)	10.8 (16.4)	0.124
ASDAS-CRP, mean (SD)	3.0 (2.0)	2.8 (1.6)	2.7 (1.5)	3.4 (2.7)	**0.000**[a,b,c]
Global VAS, mean (SD)	4.6 (2.71)	4.4 (2.7)	4.5 (2.5)	5.2 (2.8)	**0.001**[b,c]
BASDAI, mean (SD)	4.8 (6.3)	4.4 (5)	4.3 (5)	6 (8.7)	**0.004**[b,c]
BASFI, mean (SD)	4.3 (4.9)	3.7 (4.6)	4.1 (5)	5.4 (5.1)	**0.000**[b,c]
SF12 Physical component, mean (SD)	34.5 (11.6)	34.7 (12.8)	34.3 (11.5)	34.4 (9.4)	0.938
SF12 Mental component, mean (SD)	47.2 (13.8)	46.1 (14.9)	47.5 (14.1)	48.9 (11)	0.063
BASRI, mean (SD)	7.3 (3.9)	6.2 (3.7)	7.7 (3.7)	8.5 (4)	**0.000**[a,b]

* ANOVA or chi-square for continuous and qualitative variables, respectively.
[a] $p < 0.05$ between groups 0 and 1.
[b] $p < 0.05$ between groups 0 and 2.
[c] $p < 0.05$ between groups 1 and 2
antiTNF: anti-Tumor Necrosis Factors; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiology
Index; global VAS: patient's global visual analog scale; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate, DMARDs: disease-modifying antirheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; SD: Standard deviation; SpA: Spondyloarthritis.

(24.4%) suffered from one comorbidity, and 214 (28.6%) patients suffered from two or more comorbidities. In the overall population, 75.3% of the patients were men, and their mean age was 48.37 ± 12.2 years. The most prevalent comorbidities were hypertension (23.4%), hypercholesterolemia (20%) and gastrointestinal ulcer (7.2%). The prevalence of the different comorbidities are shown in Supplementary Table 2.

Table 1 presents the population baseline characteristics with regard to the number of comorbidities. At baseline, the disease duration was longer in patients with two or more comorbidities (26.3 years) than in patients with one (21.9 years) and zero (18.1 years) comorbidities.

Association between the number of comorbidities and PROs

The association between the number of comorbidities and the PROs evaluated through linear regression is shown in Table 2. We found that all PROs were increased in patients with 2 or more comorbidities in comparison with patients without comorbidities. Patients with two or more comorbidities showed an increase in the global VAS score of 0.78 (95% CI 0.52 to 1.05) points in comparison with those with 0 comorbidities and an increase of 0.79 (95% CI 0.47 to 1.10) points after adjusting for disease duration, age, sex and smoking. The BASDAI and the ASDAS also showed an increase of 1.06 (95% CI 0.54 to 1.58) points and 0.42 (95% CI 0.23 to 0.60), respectively, in patients with 2 or more comorbidities compared to those with 0 comorbidities after adjusting for confounders. Similarly, when adjusting for disease duration, age, sex and smoking, we also found an increase in the BASFI of 1.01 (95% CI 0.57 to 1.45) points in patients with 2 or more comorbidities vs. patients with 0 comorbidities.

We evaluated the change in SF12 physical and mental components depending on the number of comorbidities. The SF12 physical component decreased significantly by −1.27 (95% CI −2.40 to −0.13) points in patients with 1 comorbidity compared to those with 0 comorbidities, and it remained significant after adjusting for confounders. In patients with 2 or more comorbidities, the SF12 physical component decreased by −2.00 (95% CI −3.27 to −0.74) points in comparison with those with 0 comorbidities after adjusting for disease duration, age, sex and smoking. Finally, the SF12 mental component showed a significant increase of 1.52 (95% CI 0.26 to 2.78) points in patients with 2 or more comorbidities compared to those with 0 comorbidities, although it was not significant after adjusting for confounders.

Table 2
Association between the number of comorbidities and PROs based on individual measurements.

	Global VAS		BASDAI		ASDAS-CRP	
	Crude β (95%CI)*	β (95%) adjusted for confounders**	Crude β (95%CI)*	β (95% CI) adjusted for confounders**	Crude β (95%CI)*	β (95%) adjusted for confounders**
1 comorbidity vs. 0 comorbidities	0.21 (−0.07 to 0.49)	0.26 (−0.04 to 0.56)	0.03 (−0.43 to 0.48)	0.06 (−0.43 to 0.55)	0.09 (−0.08 to 0.25)	0.09 (−0.09 to 0.27)
2 or more comorbidities vs. 0 comorbidities	**0.78 (0.52 to 1.05)**	**0.79 (0.47 to 1.10)**	**1.12 (0.69 to 1.56)**	**1.06 (0.54 to 1.58)**	**0.49 (0.33 to 0.64)**	**0.42 (0.23 to 0.60)**
	BASFI		**SF12 Physical component**		**SF12 Mental component**	
	Crude β (95%CI)*	**β (95%) adjusted for confounders****	**Crude β (95%CI)***	**β (95%CI) adjusted for confounders****	**Crude β (95%CI)***	**β (95%) adjusted for confounders****
1 comorbidity vs. 0 comorbidities	**0.59 (0.20 to 0.98)**	0.38 (−0.03 to 0.79)	**−1.27 (−2.40 to −0.13)**	**−1.21 (−2.24 to −0.02)**	0.32 (−0.98 to 1.63)	0.27 (−1.11 to 1.63)
2 or more comorbidities vs. 0 comorbidities	**1.68 (1.31 to 2.05)**	**1.01 (0.57 to 1.45)**	**−2.23 (−3.33 to −1.14)**	**−2.00 (−3.27 to −0.74)**	**1.52 (0.26 to 2.78)**	0.88 (−0.57 to 2.33)

* Linear regression models.
** Linear regression models adjusted for disease duration, age, sex and smoking status.
ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, Global VAS: patient's global visual analog scale.

Impact of the number of comorbidities on PROs after two years of follow-up

The impact of the number of comorbidities on PROs over two years of follow-up is displayed in Fig. 1. Overall, patients with two or more comorbidities had higher scores during the two years of follow-up on the Global VAS, BASDAI, ASDAS, and BASFI and worse scores on the SF12 physical component.

Table 3 shows the results of the mixed model with random effects to evaluate the impact of the number of comorbidities on PROs after two years of follow-up. The mean global VAS, BASDAI, ASDAS, BASFI and SF12 physical components were significantly higher among patients with 2 or more comorbidities over the two years of follow-up, while patients without comorbidities showed the lowest scores. After adjusting for disease duration, age, sex and smoking, these scores remained significantly higher in the group of patients with 2 or more comorbidities, except for the SF12 physical component. PROs values per group and per timepoint are shown in Supplementary Table 3.

Finally, the percentage of patients achieving ASDAS low disease activity (ASDAS < 2.1) after 2 years of follow-up were 44.3%, 34.3% and 23.5% for patients with 0, 1 and 2 or more comorbidities, respectively ($p < 0.001$). In addition, 16.4%, 13.1% and 8.7% of patients with 0, 1 and 2 or more comorbidities, respectively, achieved ASDAS inactive disease (ASDAS < 1.3), although these differences were non-significant (Fig. 2).

Impact of the number of comorbidities on adherence to the first TNF-alpha blocker

The use of anti-TNF agents categorized by the number of comorbidities is presented in Supplementary Fig. 2. A total of 34.4%, 37.2% and 33.6% of patients with 0, 1 and 2 or more comorbidities, respectively, had ever used anti-TNF, without significant differences between groups.

The impact of the number of comorbidities on adherence to the first anti-TNF is displayed in Fig. 3. We found a higher probability of withdrawing anti-TNF in patients with 2 or more comorbidities in

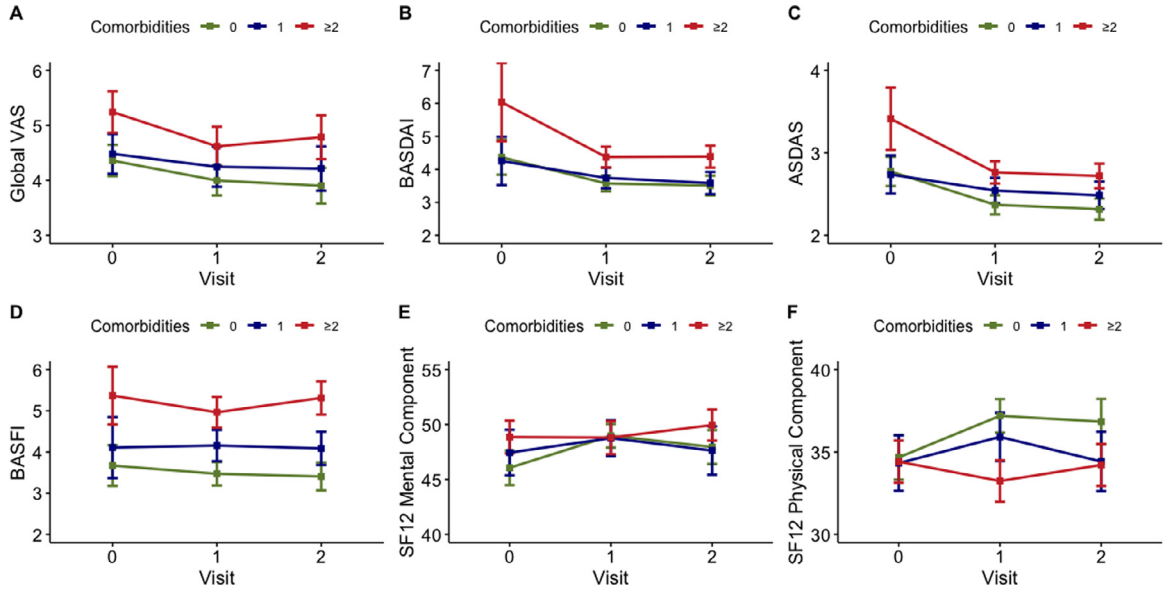

Fig. 1. Impact of the number of comorbidities on PROs over two years of follow-up.

Table 3
Impact of the number of comorbidities on PROs over two years of follow-up: mixed models for repeated measures (MMRM).

Mean scores over the 2 years of follow-up	0 comorbidities *N* = 352 mean (SD)	1 comorbidity *N* = 183 mean (SD)	≥ 2 comorbidities *N* = 214 mean (SD)	Crude MMRM	Adjusted MMRM*
Global VAS	4.1 (2.7)	4.32 (2.5)	4.89 (2.7)	< **0.001**	**0.002**
BASDAI	3.9 (3.6)	3.87 (3.4)	4.97 (5.6)	< **0.001**	**0.002**
ASDAS-CRP	2.5 (1.3)	2.59 (1.2)	2.99 (1.9)	< **0.001**	**0.001**
BASFI	3.5 (3.6)	4.12 (3.6)	5.21 (3.8)	< **0.001**	**0.002**
SF12 mental component	47.6 (12.8)	47.96 (13.2)	49.15 (10.6)	0.211	0.615
SF12 physical component	36.2 (11.4)	34.90 (11.1)	33.94 (0.2)	**0.011**	0.110

MMRM: Mixed model for repeated measures.
* Adjusted for disease duration, age, sex and smoking status
ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, Global VAS: patient's global visual analog scale.

comparison with the other two groups (38.2% vs. 26.6% vs. 25.4% for 2 or more comorbidities, 0 and 1 comorbidity, respectively), although these differences were nonsignificant (*p*-value log rank test: 0.180).

Discussion

In this prospective study, we showed that the increase in comorbidities in AS patients was associated with worse functional ability, higher disease activity, and worse mental and physical health in comparison with patients without comorbidities. These individuals also had a higher tendency of anti-TNF withdrawal than those without comorbidities.

Interest in the study of comorbidities in patients with axSpA has been growing in recent years due to their potential impact on patient well-being and prognosis. In our AS population, 53% of patients had at least one comorbidity, which is in line with previous data reported in the worldwide ASAS-COMOSPA project, where the prevalence of comorbidities was 51% [5]. Several studies have evaluated the influence of comorbidities on PROs [19–21], although most of them are cross-sectional, which prevents an evaluation of the impact of such comorbidities over time.

At baseline, patients with two or more comorbidities showed a higher frequency of men and a higher mean age and disease duration, although no differences were found between the three groups in terms of clinical characteristics or treatments. Interestingly, neither synovitis nor psoriasis were different across the three groups. A recent publication in the COMOSPA study showed that both psoriasis and peripheral involvement were associated with more cardiovascular risk factors [22]. However, that study included axSpA, peripheral SpA and psoriatic arthritis, which implies a heterogeneous population. The present study included only patients with a diagnosis of AS, which may be the reason why we did not find differences in clinical characteristics. At baseline, the only clinical features that were more prevalent in patients with two or more comorbidities were hip involvement and hip prostheses, which may be explained by the longer disease duration in this group.

We found that PROs were increased in patients with two or more comorbidities in comparison with patients without comorbidities, not only at baseline but also over two years of follow-up. At each individual visit, patients with two or more comorbidities showed an average increase of 0.79 and 1.06 in the global VAS and BASDAI, respectively, in comparison with patients without comorbidities after adjusting for disease duration, age, sex and smoking. This means that, in clinical practice, these patients will score higher on the disease activity questionnaires, leading to a lower likelihood of achieving low disease activity or remission, as it has been demonstrated in this study. In addition, patients with two or more comorbidities had higher scores after two years of follow-up on the Global VAS, BASDAI, ASDAS, and BASFI and worse scores on the SF12 physical component, as has been shown on the MMRM. One could argue that worse outcomes in patients with comorbidities are explained by a lesser use of bDMARDs in comparison with patients without comorbidities, since these conditions may influence treatment decisions [9]. However, in our study, the use of anti-TNF across the three groups was similar, suggesting that the worse PROs are not driven by a lesser use of bDMARDs.

Our results are in line with a previous study conducted by Zhao et al. [23], in which the authors found that participants with multiple comorbidities had significantly fewer absolute improvements in function and health-related quality of life after anti-TNF initiation. These results are relevant since more than 50% of patients with SpA may have comorbid diseases, leading to difficult management [24] and a poor quality of life.

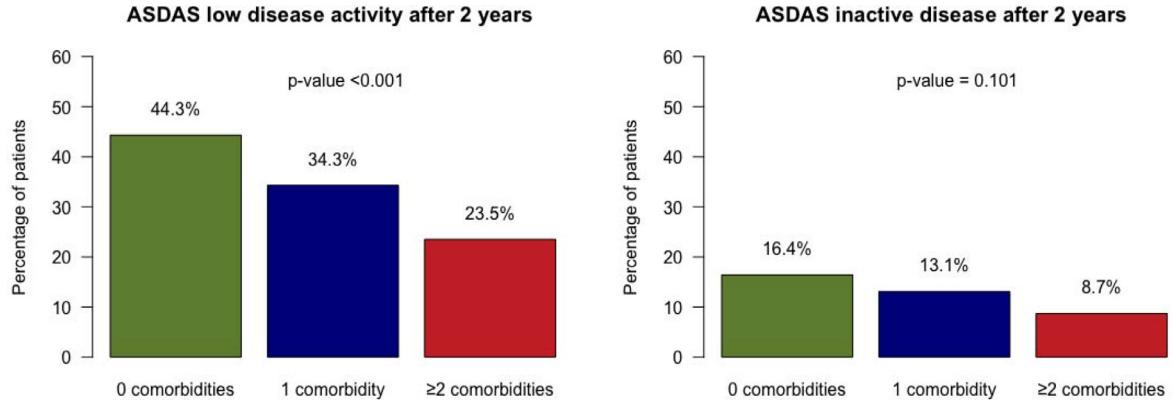

Fig. 2. ASDAS low disease activity and ASDAS inactive disease after 2 years of follow-up depending on the number of comorbidities.

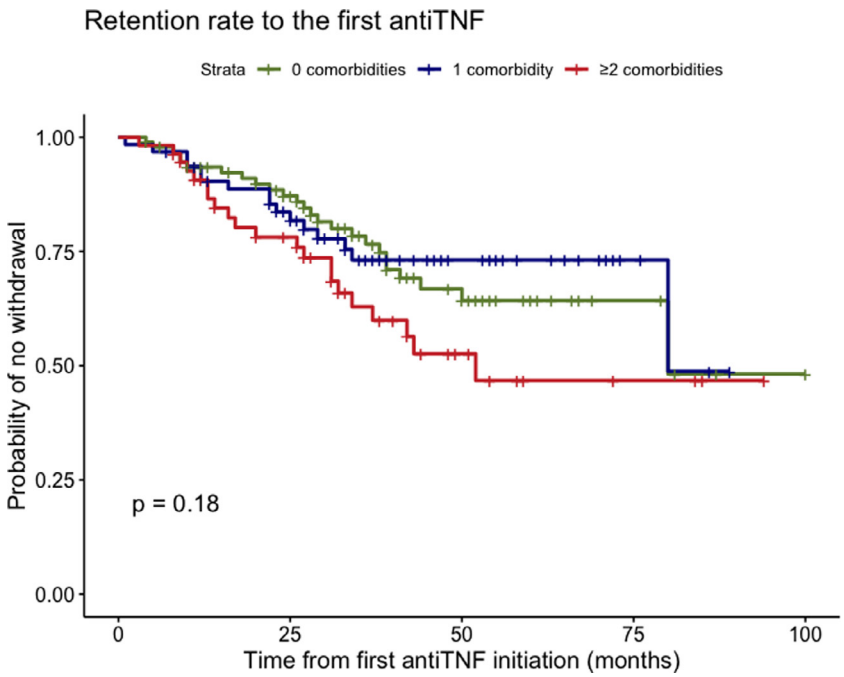

Fig. 3. Impact of the number of comorbidities on the adherence to the first anti-TNF. Kaplan-Meier curve and log-rank test.

We found a higher trend of withdrawing anti-TNF in patients with 2 or more comorbidities in comparison with the other two groups, although we did not find significant differences among the three groups. However, Zhao et al. [23] confirmed a significant difference in the retention rate to the first anti-TNF in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS), particularly notable for those with 2 and 3 or more comorbidities. Thus, our results are in line with these previous results, and the absence of significant differences in our study may be explained by the smaller sample size or the lower prevalence of anti-TNF therapy in our cohort. It should be noted that the REGISPONSER-AS registry was launched in 2004, when anti-TNF antibodies were not widely used. Thus, the number of comorbidities can be a good predictor of anti-TNF withdrawal that may be considered in clinical practice [23,25].

Our study has some limitations and strengths. One limitation is that we did not evaluate comorbidities appearing between visits, focusing only on comorbidities present at baseline. One strength of this study is the homogeneity of the population, since all of these patients had a confirmed diagnosis of AS. Another strength is that additional models adjusted for disease duration, age, sex and smoking were explored since these variables may influence both the number of comorbidities and the PROs.

In conclusion, the presence of 2 or more comorbidities in patients with AS was associated with worse scores on the outcome measures after two years of follow-up than in patients without comorbidities. Although the three groups showed a similar use of anti-TNF alpha, a greater tendency of discontinuation of the first anti-TNF was observed in patients with 2 or more comorbidities. We have expanded previous observations on the important contribution of comorbid conditions to patient-reported axSpA measures.

Data sharing

Data are available from the authors upon reasonable request with permission of the REGISPONSER scientific committee.

Consent for publication

All authors have approved the final manuscript and given their consent for publication.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

M. Ángeles Puche-Larrubia: Formal analysis, Data curation, Writing – original draft. **Lourdes Ladehesa-Pineda:** Writing – original draft, Writing – review & editing. **Ignacio Gómez-García:** Writing – original draft, Writing – review & editing. **Pilar Font-Ugalde:** Visualization, Writing – original draft, Writing – review & editing. **Alejandro Escudero-Contreras:** Writing – original draft, Writing – review & editing. **Eduardo Collantes-Estévez:** Visualization, Formal analysis, Writing – review & editing. **Clementina López-Medina:** Conceptualization, Visualization, Formal analysis, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2021.12.007.

References

[1] Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390:73–84.
[2] Michelena X, López-Medina C, Marzo-Ortega H. Non-radiographic versus radiographic axSpA: what's in a name? Rheumatology (Oxford) 2020;59:18–24.
[3] Medina LC, Molto A. Comorbidity management in spondyloarthritis. RMD Open 2020;6:e001135.
[4] Exarchou S, Lie E, Lindström U, et al. Mortality in Ankylosing Spondylitis: results from a nationwide population-based study. Ann Rheum Dis 2016;75:1466–72.
[5] Moltó A, Etcheto A, van der Heijde D, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis 2016;75:1016–23.
[6] Zhao SS, Robertson S, Reich T, et al. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. Rheumatology (Oxford) 2020;59:47–iv57.
[7] Bremander A, Petersson IF, Bergman S, et al. Population-based estimates of common comorbidities and cardiovascular disease in Ankylosing spondylitis. Arthritis Care Res 2011;63:550–6.
[8] Maxwell LJ, Zochling J, Boonen A, et al. TNF-alpha inhibitors for Ankylosing Spondylitis. Cochrane Database Syst Rev 2015;18:Cd005468.
[9] Lindström U, Olofsson T, Wedrén S, et al. Impact of extra-articular spondyloarthritis manifestations and comorbidities on drug retention of a first TNF-inhibitor in Ankylosing Spondylitis: a population-based nationwide study. RMD Open 2018;4:e000762.
[10] Dougados M, Linden S, der van, et al. The European spondylarthropathy study group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218–27.
[11] Collantes E, Zarco P, Muñoz E, et al. Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER) – extended report. Rheumatology 2007;46:1309–15.
[12] 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.
[13] Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in Ankylosing spondylitis. Ann Rheum Dis 2003;62(127):32.
[14] Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in Ankylosing Spondylitis: the bath Ankylosing Spondylitis disease activity index. J Rheumatol 1994;21:2286–91.
[15] Lukas C, Landewé R, Sieper J, et al. Assessment of SpondyloArthritis international society. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with Ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.
[16] Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in Ankylosing Spondylitis: the development of the bath Ankylosing Spondylitis functional index. J Rheumatol 1994;21:2281–5.
[17] MacKay K, Mack C, Brophy S, et al. The bath Ankylosing Spondylitis radiology index (BASRI): a new, validated approach to disease assessment. Arthritis Rheum 1998;41:2263–70.
[18] 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.
[19] Zhao SS, Jones GT, Macfarlane GJ, et al. Association between comorbidities and disease activity in axial spondyloarthritis: results from the BSRBR-AS. Rheumatology (Oxford) 2021;60(7):3189–98.
[20] Fernández-Carballido C, Martín-Martínez MA, García-Gómez C, et al. Impact of comorbidity on physical function in patients with Ankylosing Spondylitis and psoriatic arthritis attending rheumatology clinics: results from a cross-sectional study. Arthritis Care Res (Hoboken) 2020;72(6):822–8.
[21] Redeker I, Callhoff J, Hoffmann F, et al. The prevalence and impact of comorbidities on patients with axial spondyloarthritis: results from a nationwide population-based study. Arthritis Res Ther 2020;22(1):210.
[22] López-Medina C, Jiménez-Gómez Y, Moltó A, et al. Cardiovascular risk factors in patients with spondyloarthritis from Northern European and Mediterranean countries: an ancillary study of the ASAS-COMOSPA project. Joint Bone Spine 2018;85(4):447–53.
[23] Zhao SS, Jones GT, Macfarlene GJ, et al. Comorbidity and response to TNF inhibitors in axial spondyloarthritis: longitudinal analysis of the BSRBR-AS. Rheumatology(Oxford) 2021;60(9):4158–65.
[24] Baillet A, Gossec L, Carmona L, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis 2016;75:965–73.
[25] Lindström U, Olofsson T, Wedrén S, et al. Impact of extra-articular spondyloarthritis manifestations and comorbidities on drug retention of a first TNF-inhibitor in Ankylosing Spondylitis: a population-based nationwide study. RMD Open 2018;4:e000762.