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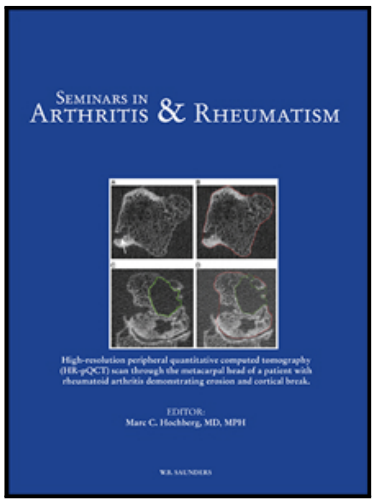

Cardiovascular and disease-related features associated with extra-articular manifestations in axial spondyloarthritis. A multicenter study of 888 patients

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PII: S0049-0172(22)00147-0
DOI: https://doi.org/10.1016/j.semarthrit.2022.152096
Reference: YSARH 152096

To appear in: *Seminars in Arthritis & Rheumatism*

Please cite this article as: Javier Rueda-Gotor , Iván Ferraz-Amaro , Fernanda Genre , Iñigo González Mazón , Alfonso Corrales , Virginia Portilla , Javier Llorca , Mario Agudo-Bilbao , Elena Aurrecoechea , Rosa Expósito , Vanesa Hernández-Hernández , Juan Carlos Quevedo-Abeledo , Carlos Rodríguez-Lozano , Clementina Lopez-Medina , María Lourdes Ladehesa-Pineda , Santos Castañeda , Esther F. Vicente , Cristina Fernández-Carballido , M Paz Martínez-Vidal , David Castro-Corredor , Joaquín Anino-Fernández , Diana Peiteado , Chamaida Plasencia-Rodríguez , María Luz García Vivar , Eva Galíndez-Agirregoikoa , Esther Montes Perez , Carlos Fernández Díaz , Ricardo Blanco , Miguel Ángel González-Gay , Cardiovascular and disease-related features associated with extra-articular manifestations in axial spondyloarthritis. A multicenter study of 888 patients, *Seminars in Arthritis & Rheumatism* (2022), doi: https://doi.org/10.1016/j.semarthrit.2022.152096

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Graphical abstract

Cardiovascular and disease-related features associated with extra-articular manifestations in axial spondyloarthritis. A multicenter study of 888 patients

Characteristics of patients with axSpA and EAMs (AAU, PSO or IBD) compared with AxSpA with no EAMs

	≥ 1 EAM (n=295)	≥ 2 EAM (n=36)	PSO (n=96)	AAU (n=177)	IBD (n=57)
Cardiovascular features	• ↑ CV events** (7% Vs 4%, p=0.032) • ↑ cIMT * (661±155 µm Vs 637±139 µm, p=0.024)	• ↑ CV events ** (11% Vs 4%, p=0.022)	• ↑ CV events ** (9% Vs 4%, p=0.048 • ↑ carotid plaques * (39% Vs 30%, p=0.038)	• ↑ cIMT * (665±156 µm Vs 637±139 µm, p=0.042)	• None

	PSO (n=96)	AAU (n=177)	IBD (n=57)
Disease-related features	• ↑ history of synovitis (50% Vs 33%, p=0.000) • ↑ History of dactilitis (13% Vs 6%, p=0.001) • ↓ HLA B27 (56% Vs 70%, p=0.003) • ↑ ESR at diagnosis (11 mm/1st hour Vs 6 mm/1st hour, p=0.024) • ↑ glucocorticoids (23% Vs 11%, p=0.002) • ↑ TNF inhibitors (50% Vs 35%, p=0.007) • ↑ DMARDs (53% Vs 30%, p=0.001	• ↑ Disease duration (20 years Vs 13 years, p=0.000) • ↑ Severe sacroiliitis (69% Vs 49%, p=0.000) • ↑ Diagnosis delay (3 years Vs 2 years, p=0.041) • ↑ HLA B27 (82% Vs 70%, p=0.000) • ↓ NSAIDs (75% Vs 82%, p=0.014) • ↑ DMARDs (46% Vs 30%, p=0.000	• ↓HLA B27 (46% Vs 70%, p=0.002) • ↑ ESR at diagnosis (19 mm/1st hour Vs 6 mm/1st hour, p=0.045) • ↓ NSAIDs (70% Vs 82%, p=0.004) • ↑ DMARDs (54% Vs 30%, p=0.006) • ↑ glucocorticoids (21% Vs 11%, p=0.032) • ↑TNF inhibitors (54% Vs 35%, p=0.003)

ABSTRACT

Objectives. To determine the potential impact of extra-articular manifestations (EAMs) on disease characteristics and cardiovascular (CV) risk in patients with axial spondylarthritis (axSpA).

Methods. This is a cross-sectional study from the AtheSpAin cohort, a Spanish multicenter cohort to study atherosclerosis in axSpA. Data on the history of CV events, subclinical carotid atherosclerosis, and disease-related features, including EAMs, were collected.

Results. 888 axSpA patients were recruited. Concomitant acute anterior uveitis (AAU), psoriasis (PSO), and inflammatory bowel disease (IBD) were present in 177 (19.9%), 96 (10.8%), and 57 (6.4%) patients, respectively. When compared with axSpA patients without EAMs, a significant increase in past CV events was observed in patients with PSO (9% versus 4%, p=0.048) and in those with at least one EAM (7% versus 4%, p=0.032) or with more than one EAM (11% versus 4%, p=0.022). The frequency of carotid plaques and the values of cIMT were higher in patients with EAMs than in those without EAMs, although only the univariable analysis for carotid plaques in patients with PSO (39% versus 30%, p=0.038) and for cIMT in patients with AAU (665 ± 156 microns versus 637 ± 139 microns, p=0.042) and those with at least one EAM (661 ± 155 microns versus 637 ± 139 microns, p=0.024) showed significant results. In addition, patients with PSO or IBD were found to have specific disease-related features, such as higher ESR at diagnosis, and more frequent use of glucocorticoids and TNF inhibitors than those without EAMs. Also, PSO patients had more commonly peripheral involvement and those with AAU more severe radiographic damage than those without EAMs. The frequency of HLA B27 was higher in patients with AAU and lower in those with PSO or IBD compared to those without EAMs.

Conclusion. Patients with axSpA and EAMs, in addition to displaying their own disease-related features, are likely to have an increased CV risk that appears proportional to the number of EAMs and could be related to proatherogenic factors other than traditional CV risk factors. such as the inflammatory load and the use of glucocorticoids.

Keywords: Ankylosing spondylitis, Non-radiographic spondyloarthritis, Atherosclerosis, Cardiovascular, extra-articular manifestations, psoriasis, inflammatory bowel disease, uveitis

INTRODUCTION

Axial spondyloarthritis (axSpA) is an immune-mediated inflammatory disease (IMID) characterized by chronic back pain with an onset before the age of 45 years. It encompasses both patients with radiographic evidence of sacroiliitis, who fulfill the 1984 Modified New York criteria for ankylosing spondylitis (AS), and others without radiographically definite sacroiliitis, classified as non-radiographic axSpA (nr-axSpA) [1]. In addition to musculoskeletal manifestations such as sacroiliac inflammation, peripheral arthritis, or enthesitis, extra-articular manifestations (EAMs) comprising acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis (PSO) frequently occur in these patients. A recent meta-analysis assessing EAMs in AS and nr-axSpA found a comparable prevalence of PSO (10.2% versus 10.9%), and IBD (4.1% versus 6.4%), while AAU was slightly more prevalent in AS (23.0% versus 15.9%) [2].

In addition to sharing common inflammatory pathways with immune dysregulation, IMIDs are also characterized by an increased risk of developing comorbid disorders linked to inflammation, highlighting the incidence of cardiovascular (CV) diseases. Widespread evidence shows accelerated atherosclerosis in different IMIDs such as rheumatoid arthritis (RA), axSpA, PSO, or IBD [3]. The prevalence of carotid plaques and the increase of carotid intima-media wall thickness (cIMT) measured by carotid ultrasound, both considered a reliable expression of subclinical atherosclerosis [4], are increased in these patients compared to the general population [5–8]. A higher risk of CV morbidity has also been reported in meta-analysis analyzing CV events in these conditions [9–12]. However, whether the coexistence of PSO, IBD, or AAU confers additional CV risk on axSpA patients remains unknown. This is a relevant pending issue that, if confirmed, could allow us to identify a subset of patients with AxSpA at higher risk, candidates for stricter preventive interventions.

The presence of EAMs has been suggested to determine specific disease characteristics in axSpA patients, although the data in this regard are controversial. While some authors have reported greater disease activity and worse mobility and functional status in patients with AS accompanied by PSO [13][14], IBD[14][13], or AAU[15][16], other studies did not find such differences [17][18]. Conflicting results have

also been reported on the influence of EAMs on radiographic damage. As first described by McEwen and colleagues in 1971, Helliwell et al. reported less severe structural damage in 34 AS patients with PSO compared to 91 classic AS [19]. Although these findings were also reported in the large multicenter Ibero-American RESPONDIA cohort [20], other authors did not confirm this finding in later studies [17,18]. Contrary to reports by other authors [17,21], AAU was independently associated with more severe radiographic damage in a cross-sectional study with 311 patients with AS [22]. The genetic background of AS patients with and without EAMs has also been a matter of controversy, with the HLA B27 status varying across the different studies depending on the coexistence of PSO, IBD, or UAA [13,17].

The AtheSpAin study is a large Spanish multicenter cohort designed to analyze atherosclerotic disease in axSpA. We have recently assessed potential disease-related pro-atherogenic factors in these patients [23]. The present study aimed to elucidate the influence of coexisting EAMs on disease characteristics and CV risk in patients with axSpA from the AtheSpAin cohort.

MATERIALS AND METHODS

2.1 Patients

This is a cross-sectional analysis of the AtheSpAin cohort, a Spanish multicenter cohort designed to study atherosclerosis in axSpA. For this, consecutive patients older than 18 years who met the radiographic definitions of AxSpA (r-axSpA) and nr-axSpA according to the ASAS criteria [1] were recruited for six years (2013-2019) in 10 different Spanish hospitals.

Two clinical indexes of disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI, and Ankylosing Spondylitis Disease Activity Score, ASDAS), a functional status index (Bath Ankylosing Spondylitis Functional Index, BASFI), a metrologic index (Bath Ankylosing Spondylitis Metrology Index, BASMI), an enthesitis index (Maastricht Ankylosing Spondylitis Enthesitis Score -MASES) [24–28], and the presence of synovitis were evaluated in all patients at the time of carotid US assessment. Waist circumference, body mass index, and blood pressure data were also obtained at the time of the study.

We reviewed information on the history of extra-articular manifestations including PSO, IBD, and AAU diagnosed respectively by dermatologists, gastroenterologists, ophthalmologists, or by general practitioners. It was also the case for information on hip involvement, synovitis, enthesitis, HLA-B27 status, disease duration, and therapy from the disease diagnosis. Data on the history of traditional CV risk factors, chronic kidney disease (defined by an estimated glomerular filtration rate below 60 mL/min per 1.73 m2), and CV events (ischemic heart disease, congestive heart failure, ischemic stroke, and peripheral artery disease) were also assessed.

Identification of patients with serum C-reactive protein (CRP) levels greater than 3 mg/L at the time of diagnosis, serum levels of CRP and erythrocyte sedimentation rate (ESR) both at the time of recruitment and at disease diagnosis, and serum lipid levels at the time of the study were reviewed. Structural damage was assessed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [29], and the presence of syndesmophytes on spinal radiographs. Patients also underwent a standard anteroposterior plain radiograph of the pelvis to classify the patients as radiographic or nr-axSpA and to assess the grade and symmetry of the radiological sacroiliitis. We obtained a subject's written consent in all the cases. The study was approved by the local Ethics Committee of Hospital Universitario Marques de Valdecilla and subsequently for Ethics Committees of the other centers.

2.2 Carotid US examination

The Carotid US examination was performed according to the same protocol in the participating hospitals. It included the measurement of cIMT in the common carotid artery and the detection of focal plaques in the extracranial carotid tree following the Mannheim consensus [30]. Plaque was defined as a focal protrusion at least cIMT >1.5 mm in the lumen, protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching >0.5 mm [30]. The cIMT was determined as the average of three measurements in each common carotid artery, and the final cIMT was the largest average cIMT (left or right).

2.3 Statistical analysis

Demographic and clinical characteristics in patients with axSpA were described as mean (standard deviation) or percentages for categorical variables. For non-normally distributed continuous variables, data

were expressed as median and interquartile range (IQR). Univariable differences between subgroups of axSpA were assessed through the student's t, Mann-Whitney U, χ2 or Fisher's exact tests according to normal distribution or number of subjects. Multivariable linear and logistic regression analysis, adjusting for confounders (age, sex, disease duration and ratio r-axSpA/nr-axSpA), was assessed to analyze differences between patients with axSpA according to EAMs. All the analyses used a 5% two-sided significance level and were performed using Stata software, version 17/SE (StataCorp, College Station, TX, USA). P-values <0.05 were considered statistically significant.

RESULTS

A total of 888 patients with AxSpA were included in the present study. In this regard, 593 did not have coexisting EAMs, while concomitant AAU, PSO, and IBD were present in 177 (19.9%), 96 (10.8%), and 57 (6.4%) patients, respectively.

3.1 Disease-related characteristics of axSpA patients with and without EAMs

The main disease-related data of patients without EAMs and those with PSO, IBD, and AAU and the differences observed among them are summarized in table 1.

3.1.1. Axial Spondyloarthritis with Psoriasis.

Patients with coexisting PSO showed higher ESR levels at diagnosis [11 (5-26) mm/1st hour versus 6 (3-13) mm/1st hour, p=0.024) as well as a more prevalent history of synovitis (50 % versus 33%, p=0.000) and dactylitis (13 % versus 6%, p=0.001) than those without EAMs. Remarkably, these findings were not associated with higher disease activity or worse mobility and functional status at the time of the study. There were no differences in the radiographic features, except for a trend for a more frequent asymmetric sacroiliitis in patients with PSO (23% versus 16%, p=0,075), and a lower frequency of HLA B27 (56% versus 70%, p=0.003). However, substantial differences were observed between the two groups in the drugs used, with a higher rate of prescription of prednisone (22% versus 11%, p=0.002), DMARDs (53% versus 30%, p=0.001), and TNF-alpha inhibitors (50% versus 35%, p=0.007) in psoriatic patients.

3.1.2. Axial Spondyloarthritis with inflammatory Bowel Disease.

Only two differences related to disease characteristics were observed in the group of axSpA plus IBD when compared with those without EAMs: a more intense inflammatory response at diagnosis measured by serum levels of ESR [19 (8-42) mm/1st hour versus 6 (3-13) mm/1st hour, p=0.045) and a lower frequency of HLA B27 (46% versus 70%, p=0.002). In a similar way to what was observed in PSO, patients with concomitant IBD also received more prednisone (21% versus 11%, p=0.032), DMARDs (54% versus 30%, p=0.006), and TNF-alpha inhibitors (54% versus 35%, p=0.003) than those without EAMs. As expected, they were had fewer NSAID prescriptions (70% versus 86%, p=0.004).

3.1.3. Axial Spondyloarthritis with acute anterior uveitis

We observed some remarkable peculiarities in axSpA patients with co-existing AAU when compared to those without EAMs. In this regard, patients with AAU were characterized by a longer delay in diagnosis [3 (0-10) years versus 2 (0-7) years, p=0.041] and longer disease duration, both since first symptoms [20 (11-30) years versus 13 (5-22) years, p=0,000] and since diagnosis [13 (7-23) years versus 7 (2-15) years, p=0.000]. These patients also had a more severe structural damage measured by the prevalence of syndesmophytes (44% versus 35%, p=0.008) and severe sacroiliitis (69% versus 49%, p=0.000), although significant differences after adjusting for age, disease duration, and AS/nr-axSpA ratio persisted only for the latter. Patients with axSpA accompanied by AAU also showed a non-significant trend for a higher mobility limitation measured by BASMI (2.9 ± 1.9 versus 2.7 ± 2.1, p=0.063) and a more prevalent HLA B27 status (82% versus 70%, p=0.000). Finally, this group used DMARDs (46% versus 30%, p=0.000), especially sulfasalazine (35% versus 18%, p=0.000), more frequently and NSAIDs less often (75% versus 82%, p=0.014) than axSpA patients without EAMs.

3.2 Cardiovascular profile of axSpA patients with and without EAMs

We compared CV data in patients with axSpA without EAMs with those with coexisting PSO, IBD, and AAU, and also with patients with at least one and more than one concurrent EAM (table 2).

3.2.1. Axial Spondyloarthritis with Psoriasis.

In comparison with axSpA without EAMs, patients with axSpA and PSO were characterized by a higher prevalence of obesity (27% versus 22%, p=0.005) and a non-significant trend for a more frequent prescription of statins (20% versus 15%, p=0.067) after adjusting for age and sex. Carotid plaques, either unilateral or bilateral as well as the presence of bilateral carotid plaques were more prevalent in these patients (39% versus 30%, p=0.038, and 20% versus 14%, p=0,043, respectively), although these differences did not remain statistically significant in the multivariable analysis. In addition, a non-significant trend for a higher carotid IMT was observed in the crude analysis (664 ± 170 microns versus 637 ± 139 microns, p=0.092). Patients with PSO showed a more common history of CV events (9% versus 4%, p=0.01), which was statistically significant even after adjusting for age and sex, mainly at the expense of ischemic heart disease (6% versus 2%, p=0.022) and ischemic stroke (4% versus 0%, p=0.009).

3.2.2. Axial Spondyloarthritis with inflammatory Bowel Disease.

No differences between axSpA without EAMs and axSpA with IBD were observed concerning CV data at the time of study and traditional CV risk factors, except for a more frequent smoking habit observed in those with axSpA without EAMs (21% versus 36%, p=0.028). Carotid plaques were more common in patients with IBD (37% versus 30%, p=0.53), even when considering only its bilateral presence (18% versus 14%, p=0.26), although without a statistically significant difference. There was no difference between both groups concerning past CV events.

3.2.3. Axial Spondyloarthritis with Acute Anterior Uveitis

Axial SpA patients with AAU and those AxSpA patients without EAMs had comparable blood pressure and lipids values at the time of the study, and a similar prevalence of classic CV risk factors. We did not observe difference in the prevalence of carotid plaques in both groups. Carotid IMT was, however, higher in patients with those with IBD in the crude analysis (665 ± 156 microns versus 637 ± 139 microns, p=0.042), although this finding did not persist statistically significant after adjustment for age and sex. Besides, CV events showed a non-significant higher prevalence in this group of patients (7% versus 4%, p=0.17)

3.2.4. Axial spondyloarthritis with at least one or two or more extra-articular manifestations.

No differences were observed between patients with and without EAMs regarding CV data collected at the time of the study and data on traditional CV risk factors, except for a lower prevalence of smokers in the group of axSpA and any EAM (27% versus 36%, p=0.008). Although 37% and 18% of patients with any EAM showed unilateral/bilateral and bilateral carotid plaques respectively, compared with 30% and 14% of patients without EAMs, this difference was not statistically significant. Likewise, the increase of cIMT observed in these patients (661 ± 155 microns versus 637 ± 139 microns, p=0.024) was not significant in the multivariable analysis. In the same line, the assessment of subclinical atherosclerosis in patients with at least two EAMs yielded a non-significant increase in the prevalence of carotid plaques (38% versus 30%, p=0.58) and the cIMT (659 ± 143 microns versus 637 ± 139 microns, p=0.58) when compared with those without EAMs. However, the prevalence of past CV events was significantly higher in the multivariable analysis in patients with at least one EAM (7% versus 4%, p=0.032) and in those with two or more EAM (11% versus 4%, p=0.022). Specifically, ischemic stroke (3% versus 0%, p=0.009) and ischemic heart disease (9% versus 2%, p=0.021) were more frequent in these groups of patients when compared with those who had no EAMs.

DISCUSSION

The present study shows for the first time an increased CV risk in patients with axSpA and concomitant EAMs, which appears to be proportional to the number of coexisting EAMs. Atherosclerotic CV events were reported in 7% and 11% of axSpA patients who had at least one or two or more EAMs respectively, in contrast to 4% of patients with axSpA without EAMs. The individualized analysis showed a higher frequency of CV events in PSO and an increased trend to develop CV events in AxSpA patients with AAU. Our data showed increased subclinical atherosclerotic in patients with EAMs. However, only the univariable analysis assessing the prevalence of carotid plaques in PSO patients and the cIMT in patients with any EAM showed statistically significant differences.

Chronic inflammatory diseases, including axSpA [10], PSO [11], or IBD [12] are known to be associated with a higher risk of CV events due to an accelerated atherosclerosis process. In axSpA specifically, Peters et al

reported in 2010 an increased cIMT in 59 AS patients compared with 30 healthy controls [31], a finding subsequently confirmed by Bodnar et al [32], who also observed impaired flow-mediated vasodilation and increased pulse-wave velocity indicating abnormal endothelial function and increased aortic stiffness, respectively. These findings, together with the higher prevalence of carotid plaques observed in patients with axSpA [6], point towards an early atherosclerotic disease in this condition. The 2015/2016 EULAR recommendations for CV disease risk management recognized that CV disease risk is elevated in patients with inflammatory joint disorders including AS and highlighted the importance of achieving tight control of traditional CV risk factors and disease activity to minimize the risk [33]. However, little is known about the CV impact of coexisting IMIDs in chronic inflammatory arthropathies, and no recommendations have been made in this regard so far. PSO was a disease-related feature associated with carotid plaques in a study that included 149 patients with axSpA from northern Spain [6]. However, Giollo et al. failed to demonstrate a link between subclinical atherosclerosis and EAMs in 66 patients with SpA [34]. Regarding the AAU, the data are also scarce and contradictory. Berg et al reported carotid plaques associated with a history of uveitis in a cross-sectional study evaluating 159 AS patients [16]. This observation was not confirmed by other authors [34,35]. However, in line with the higher prevalence of cardiovascular events observed in our study, a recent retrospective cohort study of 5,905 patients with AS from the Taiwan National Database reported an association between AAU and the development of acute myocardial infarction [36]. The proatherogenic effect of EAMs in patients with axSpA may be less evident than in other well-established IMIDs, such as cutaneous PSO and IBD, where the atherosclerotic disease appears to be related to the extent of skin involvement [11] or the activity of the disease [37]. Certainly, in patients with AxSpA, concomitant severe PSO is unusual, and the therapies used in this condition, such as TNF inhibitors, help to keep skin and intestinal involvement under control. However, the role of EAMS in the development of accelerated atherosclerosis in AxSpA is supported by the fact that in our series we did not observe differences with respect to classic CV risk factors in patients with and without EAMs. The only exception was found in patients with AxSpA associated with PSO who showed a higher prevalence of obesity and a non-significant trend toward more statin prescriptions. This finding is in line with a recent analysis of the

ASAS-COMOSPA registry [38], although this study also found a higher prevalence of hypertension and diabetes mellitus in these patients. Taken together, our results point to the existence of proatherogenic factors other than traditional CV risk factors implicated in the increased CV risk of AxSpA patients with EAMs. In this regard, the prescription of glucocorticoids and serum levels of ESR at diagnosis were higher in axSpA patients with IBD or PSO. The ESR, considered a faithful reflection of the inflammatory status, has been related to CV risk both in the general population [39] and in patients with IMIDs [40], similar to what happens with the use of glucocorticoids [41]. Both factors were recently associated with clinical and subclinical atherosclerosis in axSpA patients from the AtheSpAin cohort [23]. Furthermore, our findings are consistent with a recent retrospective study reporting a higher mortality rate associated with concurrent EAMs in AS [42].

In our series, AxSpA patients with coexisting PSO showed more severe peripheral articular involvement, with a higher prevalence of arthritis (50 % versus 33%, p=0.000) and dactylitis (13% versus 6%, p=0.001) than those without EAMs. This finding is consistent with data from the multicentric prospective cohort DESIR [43], which found more swollen joints over time in these patients. Likewise, Feld et al. observed more severe peripheral structural damage in patients with psoriatic axSpA in a retrospective analysis of two longitudinal observational cohorts from Toronto [18]. We did not observe differences in terms of radiographic severity in patients with PSO measured by the mSASSS index and radiological sacroiliitis grading. This finding is in line with that described by the well-characterized cohorts of OASIS [17] and Toronto [18], but it differs from the data of the RESPONDIA group [20] and from the first studies that, during the last century, found less severe changes in psoriatic AS compared with classic AS [19,44]. Differences in disease characteristics between these studies could partially explain such a discrepancy. Classic AS patients from the RESPONDIA cohort had a longer disease duration and a higher proportion of men, features associated with structural damage [20]. Besides, all psoriatic patients included in the pioneering study by McEwen et al. had involvement of distal interphalangeal joints, suggesting a predominantly peripheral pattern [44]. However, we agree with these studies in observing a trend towards a more asymmetric sacroiliitis associated with the presence of PSO. The HLA B27 status was less frequent

in the group of co-occurring PSO from our series (56% versus 70%, p=0.003), similar to what has been reported in other series [17,43].

Concerning AAU, its coexistence in patients with axSpA from our series pointed towards a more severe disease. Patients with AAU were characterized by longer disease duration, a trend towards a higher BASMI punctuation, and more severe structural damage measured by the severity of the radiological sacroiliitis and the prevalence of syndesmophytes, although only the former achieved statistical significance following adjustment for counfunding factors (69% versus 49%, p=0.000). As far as we are concerned, a higher degree of sacroiliitis, a feature of disease severity correlated with cumulative inflammation [45] and osteoporotic fracture risk [46], has not been reported in these patients so far, while studies analyzing radiographic spinal changes have yielded conflicting results. A cross-sectional study with 311 AS patients also found an association between AAU and radiographic damage measured by BASRI [22], whereas another cross-sectional study including 531 Taiwanese AS patients [21] and a longitudinal study conducted in the OASIS cohort [17] failed to demonstrate such a link. As expected, the prevalence of HLA B27 was higher in axSpA patients with concurrent AAU (82% versus 70%, p=0.000).

In addition to the aforementioned increase in ESR at diagnosis, the only differentiating characteristic observed in axSpA patients with IBD was the prevalence of HLA B27, which was lower than that observed in axSpA patients without EAMs (46% versus 70%, p=0.002). This finding was also reported in the OASIS cohort (73.3% versus 85.3%, p=0.26), although without reaching statistical significance.

Remarkably, BASDAI, ASDAS, BASMI, and BASFI were comparable between axSpA patients with and without EAMs in our series. This result agrees with Essers et al., who also found no differences in this regard in the longitudinal OASIS cohort, although it differs from data reported by other authors who described higher disease activity, mobility limitation, or functional disability in patients with concurrent EAMs [13,14,16].

The present study has several limitations. Its cross-sectional design only allows us to identify differences among groups of patients, without establishing the causes of such findings. We are also aware that the results obtained in the group of patients with past CV events should be interpreted with caution. The

multicentric design may be another limitation, mainly regarding the collection of observer-dependent data such as the presence of subclinical atherosclerosis. Nevertheless, the US exam was performed in all cases by rheumatologists trained in ultrasonography and following the same criteria to minimize the variability.

In conclusion, our results indicate that axSpA patients are likely to have a higher CV risk in the presence of concomitant EAMs. Remarkably, the increased risk of CV events appears to be proportional to the number of concurrent EAMs and can be mediated by pro-atherogenic factors other than traditional risk factors, like the inflammatory burden and glucocorticoid use. Besides, the present study contributes to better characterizing axSpA patients with concomitant EAMs, highlighting differences in the degree of the inflammatory response and the HLA B27 status, as well as in the peripheral involvement in patients with PSO, or the radiographic damage in AAU.

Declarations of interest: none.

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Table 1. Main sociodemographic, clinical, laboratory and radiological differences between axSpA patients with and without EAMs

	axSpA without EAMs (n=593)	axSpA with PSO (n=96)	P [1]	axSpA with IBD (n=57)	P [2]	axSpA with AAU (n=177)	P [3]	P[3]*
Men/Women, n	390/203	76/20	0.11	42/15	0.44	122/55	0.68	
Mean age (years) ±SD at the time of study	48 ± 15	49 ± 13	0.13	49 ± 10	0.54	50 ± 11	0.10	
Disease related data at time of study								
Mean disease duration, years								
Since first symptoms	13 (5-22)	13 (9-23)	0.61	13 (9-25)	0.90	20 (11-30)	**0.000** [a]	
Since diagnosis	7 (2-15)	10 (3-17)	0.16	11 (5-16)	0.43	13 (7-23)	**0.000** [a]	
ASDAS	3.8 ± 2.4	2.3 ± 1.0	0.52	2.4 ± 1.0	0.81	2.2 ± 0.9	0.36	
Inactive disease	101 (17)	14 (15)		11 (19)		27 (15)		
Low activity	131 (22)	24 (25)	0.20	7 (12)	0.69	36 (20)	0.445	
High activity	219 (37)	38 (40)		26 (46)		73 (41)		
Very high activity (>3.5)	61 (10)	6 (6)		5 (9)		12 (7)		
BASDAI	3.8 ± 2.4	3.6 ± 2.3	0.76	4.0 ± 2.3	0.99	3.8 ± 2.3	0.69	
BASDAI>4	260 (44)	41 (43)	0.85	27 (47)	0.93	86 (49)	0.48	
BASFI	3.6 ± 2.6	3.3 ± 2.5	0.63	3.8 ± 2.6	0.92	3.5 ± 2.5	0.40	
Back pain (VAS)	4 (2-6)	4 (2-6)	0.80	5 (2-6)	0.86	4 (2-6)	0.30	
BASMI	2.7 ± 2.1	2.6 ± 1.7	0.54	2.8 ± 2.0	0.29	2.9 ± 1.9	0.063	
MASES	0 (0-2)	0 (0-2)	0.92	0 (0-2)	0.58	0 (0-2)	0.32	
Syndesmophytes	206 (35)	33 (34)	0.40	23 (40)	0.19	77 (44)	**0.008** [a]	0.66
mSASSS	4 (1-15)	6 (2-13)	0.97	6 (3-23)	0.34	6 (0-16)	0.22	
Severe sacroiliitis (grade 3,4)	288 (49)	50 (52)	0.93	34 (60)	0.45	122 (69)	**0.000** [a]	**0.000**[a]
Asymetric sacroiliitis	94 (16)	22 (23)	0.075	12 (21)	0.28	21 (12)	0.21	
Current drugs								
NSAIDs, n (%)	486 (82)	83 (86)	0.58	40 (70)	**0.004** [a]	132 (75)	**0.014** [a]	
Currrent prednisone, n (%)	67 (11)	22 (23)	**0.002** [a]	12 (21)	**0.032** [a]	22 (12)	0.96	
DMARDs, n (%)	178 (30)	51 (53)	**0.001** [a]	31 (54)	**0.006** [a]	82 (46)	**0.000** [a]	
Methotrexate, n (%)	84 (14)	29 (30)	**0.000** [a]	12 (21)	0.48	28 (16)	0.62	
Sulfasalazine, n (%)	107 (18)	22 (23)	0.29	15 (26)	0.40	62 (35)	**0.000** [a]	
Anti-TNF-alpha, n (%)	194 (35)	48 (50)	**0.007** [a]	31 (54)	**0.003** [a]	60 (34)	0.73	
Secukinumab, n (%)	13 (2)	1 (1)	0.68	0 (0)	0.35	8 (5)	0.10	
Historical disease related data								
Diagnosis delay, years	2 (0-7)	2 (0-7)	0.20	2 (0-8)	0.25	3 (0-10)	**0.041** [a]	
History of synovitis	197 (33)	48 (50)	**0.000** [a]	18 (32)	0.92	58 (33)	0.91	
History of enthesitis	183 (31)	31 (32)	0.51	14 (25)	0.20	54 (31)	0.84	
History of dactilitis	33 (6)	12 (13)	**0.001** [a]	2 (4)	0.43	11 (6)	0.42	
History of hip involvement	86 (15)	17 (18)	0.78	13 (23)	0.29	36 (20)	0.15	
Extraarticular manifestations								
Uveitis	-	19 (20)		10 (18)		-		
Inflammatory Bowel Disease	-	12 (13)		-		10 (6)		

Psoriasis	-			12 (21)		19 (11)		
HLA-B27 positive	418 (70)	54 (56)	**0.003** [a]	26 (46)	**0.002** [a]	146 (82)	**0.000** [a]	
CRP at time of disease diagnosis, (mg/dL)	4.0 (1.0-11.5)	5.0 (1.7-11.5)	0.94	6 (2-16)	0.22	3 (1-11)	0.30	
CRP >3 at time of diagnosis	321 (54)	55 (57)	0.56	34 (60)	0.46	84 (47)	0.24	
ESR at the time of disease diagnosis (mm/1st hour)	6 (3-13)	11 (5-26)	**0.024** [a]	19 (8-42)	**0.045** [a]	13 (7-25)	0.99	
Drugs from the disease diagnosis								
Anti-TNF-α	46 (8)	7 (7)	0.64	6 (11)	**0.025** [a]	20 (11)	0.56	
IL-17 inhibitors	9 (2)	1 (1)	0.37	1 (2)	0.58	3 (2)	0.99	
DMARDs	86 (15)	13 (14)	0.72	9 (16)	0.36	32 (18)	0.61	

P[1] for comparison between patients with axSpA without EAMs versus axSpA with PSO
P[2] for comparison between patients with axSpA without EAMs versus axSpA with IBD
P[3] for comparison between patients with axSpA without EAMs versus axSpA with AAU
P[3]* for comparison between patients with axSpA without EAMs versus axSpA with AAU adjusted for age, disease duration and ratio r-axSpA/nr-axSpA
[a] significant variable ($p < 0.05$)

Table 2. Cardiovascular data in axSpA patients with and without EAMs

	axSpA without EAMs (n=593)	axSpA with PSO (n=96)	P[1]	P[1]*	axSpA with IBD (n=57)	P[2]	P[2]*	axSpA with AAU (n=177)	P[3]	P[3]*	axSpA with ≥1 EAMs (n=295)	P[4]	P[4]*	axSpA with ≥2 EAMs (n=36)	P[5]	P[5]*
Sex	390/203	76/20	0.11		42/15	0.44		122/55	0.68		210/85	0.10		28/8	0.18	
Mean age (years) ±SD at the time of study	48 ± 15	49 ± 13	0.13		49 ± 10	0.54		50 ± 11	0.10		50 ± 11	**0.020**		48 ± 12	0.56	
Cardiovascular data at the time of study																
Lipids																
Total cholesterol	192 ± 40	191 ± 38	0.62		186 ± 40	0.15	0.15	190 ± 39	0.48		189 ± 40	0.34		195 ± 35	0.47	
HDL-cholesterol	56 ± 17	52 ± 13	0.15	0.32	52 ± 15	0.23		54 ± 17	0.98		53 ± 16	0.25		53 ± 15	0.66	
LDL-cholesterol	117 ± 32	117 ± 35	0.98		115 ± 39	0.99		116 ± 33	0.77		116 ± 35	0.99		120 ±33	0.47	
Atherogenic ndex ≥4	215 (36)	33 (34)	0.78		22 (39)	0.98		63 (36)	0.67		103 (38)	0.79		14 (42)	0.62	
Triglycerides	123 ± 82	108 ± 60	0.45		124 ± 65	0.83		123 ± 92	0.83		120 ± 81	0.61		104 ± 62	0.17	
Statins	91 (15)	19 (20)	**0.026** [a]	0.067	5 (9)	0.45		30 (17)	0.41		142 (18)	0.34		4 (13)	0.40	
BMI>30 Kg/m2	130 (22)	26 (27)	0.14	**0.005** [a]	16 (28)	0.17	0.19	34 (19)	0.54		71 (25)	0.44		9 (26)	0.67	
Blood pressure, mm Hg																
Systolic	129 ± 18	130 ± 16	0.74		130 ± 18	0.43		131 ± 17	0.20		131 ± 17	0.26		128 ± 15	0.59	
Diastolic	79 ± 11	80 ± 9	0.36		79 ± 10	0.96		80 ± 11	0.16	0.36	80 ± 10	0.24		78 ± 8	0.55	
History of cardiovascular risk factors																
Current smoker	216 (36)	30 (31)	0.44		12 (21)	**0.023** [a]	**0.028** [a]	50 (28)	0.069	0.11	81 (27)	**0.008** [a]		9 (25)	0.27	
Dyslipidemia	193 (35)	35 (36)	0.24		16 (28)	0.65		63 (36)	0.42		104 (36)	0.36		12 (33)	0.98	
Hypertension	151 (25)	28 (29)	0.22		16 (28)	0.23		50 (28)	0.26		88 (30)	0.14		8 (22)	0.51	
Diabetes Mellitus	40 (7)	8 (8)	0.55		4 (7)	0.34		14 (8)	0.61		24 (8)	0.45		2 (6)	0.70	
Chronic Kidney Disease	15 (3)	3 (3)	0.69		2 (4)	0.99		4 (2)	0.71		7 (2)	0.89				
History of CV events, n (%)																
Total CV events	21 (4)	9 (9)	**0.010** [a]	**0.048** [a]	2 (4)	0.99		12 (7)	0.17	0.25	21 (7)	**0.017** [a]	**0.032** [a]	4 (11)	0.057	**0.022** [a]

Ischemic heart disease	14 (2)	6 (6)	**0.022** [a]	0.090	1 (2)	0.99		6 (3)	0.77		12 (4)	0.16	0.23	3 (9)	**0.044**	**0.021** [a]
Congestive heart failure	1 (0)	1 (1)	0.20		0 (0)	0.99		1 (1)	0.37		2 (1)	0.22		0 (0)	0.73	
Ischemic stroke	2 (0)	4 (4)	**0.009** [a]	**0.012** [a]	1 (2)	0.17	0.11	4 (2)	0.060	0.062	8 (3)	**0.002** [a]	**0.009** [a]	1 (3)	0.32	
Peripheral artery disease	4 (1)	0 (0)	0.99		0 (0)	0.99		2 (1)	0.35		2 (1)	0.99		0 (0)	0.62	
Carotid ultrasound																
Carotid plaques (uni/bilat)	178 (30)	38 (39)	**0.038** [a]	0.35	21 (37)	0.53		57 (32)	0.61		105 (37)	0.11	0.52	12 (38)	0.58	
Bilateral carotid plaques	83 (14)	10 (20)	**0.043** [a]	0.82	10 (18)	0.26		28 (16)	0.43		53 (18)	0.12	0.22	4 (11)	0.48	
IMT	637 ± 139	664 ± 170	0.092	0.58	636 ± 112	0.98		665 ± 156	0.042	0.60	661 ± 155	**0.024** [a]	0.49	659 ± 143	0.58	
IMT >= 900 microns	31 (5)	6 (6)	0.543		0 (0)	0.13		10 (6)	0.73		25 (8)	0.70		5 (14)	0.30	

P^1 for comparison between patients with axSpA without EAMs versus axSpA with PSO
P^1* for comparison between patients with axSpA without EAMs versus axSpA with PSO adjusted for age and sex
P^2 for comparison between patients with axSpA without EAMs versus axSpA with IBD
P^2* for comparison between patients with axSpA without EAMs versus axSpA with IBD adjusted for age and sex
P^3 for comparison between patients with axSpA without EAMs versus axSpA with AAU
P^3* for comparison between patients with axSpA without EAMs versus axSpA with AAU adjusted for age and sex
P^4 for comparison between patients with axSpA without EAMs versus axSpA with ≥1 EAMs
P^4* for comparison between patients with axSpA without EAMs versus axSpA with ≥1 EAMs adjusted for age and sex
P^5 for comparison between patients with axSpA without EAMs versus axSpA with ≥2 EAMs
P^5* for comparison between patients with axSpA without EAMs versus axSpA with ≥2 EAMs adjusted for age and sex
[a] significant variable ($p < 0.05$)