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ORIGINAL RESEARCH

Sex differential impact of comorbidities in spondyloarthritis: data from COMOSPA study

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ABSTRACT

Objectives To describe and compare the prevalence of comorbidities in female and male patients with spondyloarthritis (SpA) and to assess whether comorbidities had a different impact on disease outcomes in male and female patients.

Methods This is a post hoc analysis of the COMOrbidities in SPondyloArthritis study. Differences in comorbidities regarding sex were assessed using logistic regression models. Comorbidities were evaluated for their impact on disease outcomes (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index, European health-related quality of life questionnaire) with linear models, which included sex and comorbidity as explanatory variables and their interaction. Age and treatment with biological synthetic disease-modifying antirheumatic drugs were included as confounders.

Results We included 3982 patients with SpA (65% male, mean age 43.6 years). Male and female patients with SpA exhibited similar comorbidity profiles, except for a low prevalence of fibromyalgia in males and a higher prevalence of certain cardiovascular risk factors in males (hypertension, dyslipidaemia, renal impairment and ischaemic heart disease). Comorbidities, especially fibromyalgia, correlated with higher disease activity, decreased physical function and reduced health-related quality of life in both sexes. Some comorbidities exhibited sex-specific associations with disease outcomes. Peptic ulcers and high waist circumference had a greater impact on disease activity in females (with a higher impact in BASDAI than in ASDAS). In contrast, osteoporosis had a more pronounced effect on physical function in male patients.

Conclusions Comorbidities exert distinct influences on disease activity, physical function and health-related quality of life in male and female patients with SpA. Understanding these sex-specific effects is crucial for improving SpA management, emphasising the importance of assessing disease activity using ASDAS when comorbidities are present to mitigate sex-related disparities in disease assessment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous data reported sex differences in patients with spondyloarthritis (SpA) regarding disease characteristics and outcomes.

WHAT THIS STUDY ADDS

⇒ This study demonstrates differences in the prevalence of comorbidities in female and male patients with SpA and illustrates how comorbidities have varying impacts on disease outcomes in both sexes.

⇒ The impact of comorbidities on disease activity is lower when assessed using the Ankylosing Spondylitis Disease Activity Score compared with the Bath Ankylosing Spondylitis Disease Activity Index score.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study revealed sex differences in the prevalence of cardiovascular diseases and fibromyalgia among male and female patients with SpA.

⇒ The data from this study demonstrate significant sex-dependent variations in how certain comorbidities influence disease activity, physical function and health-related quality of life.

INTRODUCTION

Patients with spondyloarthritis (SpA) can exhibit distinct phenotypic presentations, including axial spondyloarthritis (axSpA) and peripheral spondyloarthritis. Beyond musculoskeletal manifestations, patients with SpA usually experience extra-musculoskeletal manifestations such as psoriasis, anterior uveitis and inflammatory bowel disease (IBD). Additionally, patients with SpA show a higher prevalence of comorbidities compared with the general population, particularly for specific disorders like cardiovascular disease (CVD), fibromyalgia (FM) and osteoporosis (OP).[1–3] This increased comorbidity prevalence can be attributed, in part, to shared risk factors, the consequences of systemic

inflammation or specific treatments (eg, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids).[1–3] The presence of comorbidities in SpA is associated with a diminished quality of life, elevated mortality rates, increased healthcare costs and heightened disease activity.[1–3]

CVD is a leading global cause of mortality, exhibiting notable differences between sexes. Males tend to develop CVD at a younger age and display a higher susceptibility to coronary heart disease, while females face a higher risk of stroke, typically occurring at an older age.[4 5] In contrast, OP is more prevalent among females, particularly after menopause, and fractures associated with this condition have a significant impact on overall health status.[6 7] Additionally, neoplasms and infections present significant health challenges with the potential for differing effects on an individual's health-related quality of life based on their sex.

In recent years, numerous studies have explored sex-based differences in rheumatic diseases, including SpA. Radiographic axSpA is more frequently diagnosed in males than females. However, non-radiographic forms exhibit a similar incidence in both male and female patients.[8] Females with axSpA experience a substantial delay in diagnosis, report worse disease activity scores and demonstrate lower tumour necrosis factor inhibitor efficacy and drug survival rates compared with males.[9] Conversely, males show more pronounced structural progression and elevated C reactive protein (CRP) levels than females.[8]

While data on sex differences in SpA are available, research on the differential impact of comorbidities in male and females remains limited, a gap in the literature pointed by two recent reviews.[5 9] Understanding these sex-based differences in comorbidities effects on disease activity, physical function and health-related quality of life of patients with SpA is crucial for enhancing the overall management of this condition. Therefore, the present study aims (a) to describe and compare the prevalence of comorbidities in female and male patients with SpA and (b) to assess whether comorbidities had a different impact on disease outcomes in male and female patients.

METHODOLOGY

Study population

This study constitutes a post hoc analysis of the COMOrbidities in SPondyloArthritis (COMOSPA) study, including 3982 patients diagnosed with SpA. Details of this database have been described previously.[3] Briefly, the inclusion criteria encompassed adult patients (≥18 years) fulfilling the Assessment of Spondyloarthritis International Society criteria (whether for axial or peripheral involvement), and who possessed the capacity to comprehend and complete questionnaires assessing various aspects such as disease activity, physical function and quality of life.

Assessments

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

A. Demographic and disease characteristics: sex, age, disease duration, smoking (ever), current alcohol intake (≥3 units) and body mass index (BMI, kg/m^2). History and current clinical presentation, including axial involvement, peripheral articular disease, enthesitis, dactylitis, uveitis, psoriasis, IBD and HLA-B27 antigen status.
B. Disease and health-related outcomes: disease activity was measured using two methods: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score CRP (ASDAS-CRP). Patients' functional ability was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI). The percentage of work missed was also determined using the Work Productivity and Activity Impairment Specific General Health Questionnaire (WPAI:GH). Additionally, patients' health-related quality of life was evaluated using the European health-related quality of life (EQ5D) questionnaire, which includes questions on mobility, self-care, pain, usual activities and psychological status. In this questionnaire, each question had three possible answers (1=no problem, 2=moderate problem, 3=severe problem). From these dimensions, a summary index was derived, with a maximum score of 1 indicating a better health state.[10]
C. Past and current medications: the database included information on the use of NSAIDs, conventional synthetic and biological disease-modifying antirheumatic drugs (csDMARDs and bDMARDs, respectively) and the total intake of corticosteroids was collected.
D. Comorbidities: this section covered various comorbidities, including:
    a. Cardiovascular (CV) conditions: CVD, ischaemic heart disease and stroke. CV risk factors: waist circumference (defined as a categorical variable with cut-off points based on the general male and female population, ≥102 cm in males and ≥88 cm in females),[11] and previous diagnosis of hypertension, dyslipidaemia, diabetes and renal impairment.
    b. OP: the database recorded bone mineral density and any history of vertebral or peripheral non-traumatic fractures. OP was defined using a composite index based on T-score <−2.5 SD at any location, presence of an osteoporotic fracture or previous treatment for this condition.
    c. Neoplasms: the project documented any history of colon cancer, lung cancer, skin cancer (eg, melanoma and basal cell carcinoma) and lymphoma.
    d. Infections: this category included a history of hepatitis B virus (HBV), hepatitis C virus (HCV) and severe infection requiring hospitalisation.
    e. FM: the COMOSPA study did not encompass specific criteria for identifying the presence of FM. Consequently, we subsequently categorised patients with FM comorbidity according to the

'extreme patient-reported outcome (PRO)' definition.[12] According to these criteria, FM was defined as a score ≥8 (0–10 scale) on three out of the first five BASDAI questions (morning stiffness duration was not included) based on previous reports: fatigue, spinal pain, peripheral arthritis, enthesitis and intensity of morning stiffness. Patients with more than three out of the first five BASDAI questions missing were excluded.[12] The definition of FM based on 'extreme PRO' has been used as a surrogate marker of FM in patients with axSpA in which the FM criteria were not available and has shown a great specificity for FM recognition in patients with axSpA.[12]

Statistical analysis

We summarised comorbidities and disease-related indices (activity, physical function and health-related quality of life) using absolute and relative frequencies for male and female patients separately, as well as for the whole series. Differences regarding sex were assessed using χ^2 tests and t-tests for binary and continuous variables, respectively. Despite the unbalanced sex distribution of patients observed in our cohort (65% males and 35% females), which is inherent to the disease prevalence in the studied population, the sample size (2588 males and 1394 females) ensures a proper estimation of the prevalence of comorbidities in both male and female patient groups.

To evaluate sex differences in comorbidities while adjusting for age and the use of bDMARD, we employed logistic regression models for each comorbidity separately, estimating ORs as a measure of these differences. In these logistic regression models, sex served as the response variable, and female patients and the absence of comorbidity were coded as the reference groups. Additionally, we examined the impact of comorbidities on disease parameters independently. Linear models were fitted to each index, with comorbidity and sex as explanatory variables, including their interaction (sex and comorbidities). The evaluation of the interaction term allowed us to assess the differential impact of comorbidities on outcomes for both female and male patients in a way that, given the high sample available for analyses, is robust to the imbalanced sex distribution observed in our cohort. Adjusted group means and differences were derived from these models to measure effect sizes. In the multivariate analyses, statistical significance was determined using Wald tests derived from the models. The threshold for statistical significance was set to 5%.

As a reference and to assist result interpretation, we used established criteria for defining minimal clinically important differences, which were 1 unit for BASDAI and 0.6 units for BASFI.[13–15] A clinically relevant improvement in ASDAS was defined as a decrease of at least 1.1 points,[15 16] while clinically important worsening was defined as an increase of at least 0.9 points.[17]

RESULTS

Study population by sex

Data from 3982 patients with SpA were available for analyses, comprising 2588 (65%) male and 1394 (35%) female patients. The mean patient age was 43.6 years (SD 13.9) and the average disease duration was 8.2 years (SD 9.3). Most patients presented axial involvement (88.7%) and 72.4% tested positive for HLA-B27. The mean BMI was 26.1 kg/m^2, and 46.4% of patients reported a history of smoking.

Table 1 presents a comparison of demographics and disease characteristics between male and female patients with SpA. Males were slightly younger (42.9 years) than females (45.1 years, p<0.001), were diagnosed at a younger age (33.7 vs 38.5 years, p<0.001 and showed a longer disease duration on average (9.1 vs 6.6 years, p<0.001). Male patients also presented a higher prevalence of smoking history (53.0% vs 34.2%, p<0.001) and alcohol intake (8.5% vs 3.6%, p<0.001), along with a higher rate of HLA-B27 positivity (78.7% vs 60.0%, p<0.001). BMI was similar in both patient groups (25.9 and 26.6, respectively, p<0.001).

When analysing clinical features, male patients were more likely to have axial involvement (89.7% vs 86.9%, p=0.009) while females presented a higher prevalence of peripheral articular disease (68% vs 55.7%, p<0.001), more enthesitis (41.9% vs 35.9%, p<0.001) and more dactylitis (19.9% vs 13.2%, p<0.001). As for extra-musculoskeletal manifestations, females exhibited a higher prevalence of psoriasis (29.4% vs 20.8%, p<0.001), and a higher prevalence of IBD (8.1% vs 5.3%, p<0.001), However, no significant differences emerged with regard to uveitis (table 1).

Regarding treatment approaches, no substantial differences were observed between males and females in the utilisation of NSAID therapy or bDMARDs. However, the use of csDMARDs was significantly more prevalent among female patients (65.9% vs 58.3%, p<0.001).

Finally, females presented with higher disease activity, worse physical function and worse overall health than male patients (table 1). The BASDAI score presented a significant increase in female patients, with a mean difference of 0.9 points. The ASDAS-CRP also displayed a statistically significant increase in females, although the mean difference of 0.22 units was far from clinically significant according to the established criterion (>1.1). On average, females also showed a significantly higher BASFI score (0.74 points increase), a lower EQ5D health-related quality of life index (0.07 units decrease) and a higher percentage of work missed as measured by the WPAI:GH (5.5% increase) compared with the male patients (table 1).

Comorbidities differences by sex

When analysing comorbidities, male patients presented a higher prevalence of renal impairment (2.9% vs 1.4%, p=0.005) and ischaemic heat disease (3.3% and 1.5%, p=0.001). Whereas high waist circumference (48.1%

Table 1 Demographics, disease characteristics and therapeutics features of the 3982 male and female patients with SpA included in the study

	Patients with SpA			
	Total n=3982	Males n=2588	Females n=1394	P value
Age	43.6 (13.9)	42.9 (14.1)	45.1 (13.4)	**<0.001**
Age at diagnose	35.4 (12.9)	33.7 (12.7)	38.5 (12.7)	**<0.001**
Disease duration (years)	8.2 (9.3)	9.1 (10.0)	6.6 (7.8)	**<0.001**
Body mass index	26.1 (5.7)	25.9 (5.2)	26.6 (6.5)	**<0.001**
Ever smoker	1846 (46.4%)	1370 (53.0%)	476 (34.2%)	**<0.001**
Current alcohol intake—3 units or more	269 (6.8%)	219 (8.5%)	50 (3.6%)	**<0.001**
HLA-B27 positive	2217 (72.4%)	1599 (78.7%)	618 (60.0%)	**<0.001**
NSAIDs intake history	3547 (89.6%)	2308 (89.7%)	1239 (89.3%)	0.715
Corticosteroids history	1759.8 (6934.9)	1658.9 (7407.8)	1947.1 (5956.8)	0.215
csDMARDs history	2427 (60.9%)	1509 (58.3%)	918 (65.9%)	**<0.001**
bDMARDs history	1692 (42.5%)	1098 (42.4%)	594 (42.6%)	0.911
Axial involvement	3516 (88.7%)	2309 (89.7%)	1207 (86.9%)	**0.009**
Peripheral articular disease	2378 (60.0%)	1433 (55.7%)	945 (68.0%)	**<0.001**
Peripheral enthesitis	1506 (38.0%)	924 (35.9%)	582 (41.9%)	**<0.001**
Dactylitis	617 (15.6%)	340 (13.2%)	277 (19.9%)	**<0.001**
Psoriasis	939 (23.8%)	534 (20.8%)	405 (29.4%)	**<0.001**
Uveitis	831 (21.2%)	561 (22.0%)	270 (19.6%)	0.083
Inflammatory bowel disease	246 (6.3%)	135 (5.3%)	111 (8.1%)	**<0.001**
BASDAI	3.7 (2.4)	3.4 (2.3)	4.3 (2.5)	**<0.001**
ASDAS-CRP	1.98 (1.07)	1.91 (1.07)	2.13 (1.06)	**<0.001**
BASFI	3.02 (2.67)	2.76 (2.61)	3.50 (2.71)	**<0.001**
EQ5D	0.64 (0.24)	0.67 (0.23)	0.60 (0.24)	**<0.001**
WPAI:GH	12.1 (27.8%)	10.7 (26.1%)	15.7 (31.6%)	**<0.001**

Cells show the mean and SD (between brackets) for continuous variables and absolute frequencies and percentages for binary variables. P values were calculated using t-tests (for continuous variables) or χ^2 tests (for binary variables).
Significant values are marked in bold.
ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EQ5D, European health-related quality of life questionnaire; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; WPAI:GH, Work Productivity and Activity Impairment Specific General Health Questionnaire.

vs 22.3%, p<0.001) and FM (19.6% vs 10.3%, p<0.001) were more prevalent in female patients (table 2). After controlling for age and bDMARDs use, male patients showed a significant higher probability for several comorbidities related to CVD and CV risk factors compared with females (table 2). This included hypertension (OR 1.47, 95% CI 1.23 to 1.77), dyslipidaemia (OR 1.29, 1.07 to 1.56), renal impairment (OR 2.36, 1.46 to 4.01) and ischaemic heart disease (OR 2.77, 1.72 to 4.65). There were also differences for diabetes mellitus (OR 1.27, 0.94 to 1.72) and stroke (OR 1.86, 1.00 to 3.66), although these did not reach statistical significance (p values 0.121 and 0.059, respectively). In terms of waist circumference, only 22.3% of males exceeded the general male population's cut-off point, while 48.1% of females surpassed the cut-off established for the general female population (OR 0.31, 0.26 to 0.37). Since CV comorbidities become more frequent with age, we conducted a similar analysis restricted to patients aged over 55 years, obtaining similar results (online supplemental table S1).

Regarding, non-CV comorbidities, our analyses showed that male patients with SpA exhibited a lower prevalence of FM (OR 0.47, 95% CI 0.39 to 0.57). No significant differences were observed between males and females for the rest of comorbidities analysed in our study (table 2).

Impact of comorbidities on disease outcomes according to sex

Disease activity

After statistical control for age and bDMARD use, most of the studied comorbidities were found to be significantly associated with disease activity. The most strongly

Table 2 Comparison of comorbidity prevalences between male and female patients with SpA

	Univariate				Adjusted by age and bDMARD	
	Total n=3982	Males n=2588	Females n=1394	P value	OR (95% CI)	P value
Hypertension	882 (22.3%)	590 (23.0%)	292 (21.0%)	0.166	1.47 (1.23 to 1.77)	**<0.001**
Diabetes	219 (5.5%)	147 (5.7%)	72 (5.2%)	0.488	1.27 (0.94 to 1.72)	0.121
Dyslipidaemia	656 (16.7%)	438 (17.1%)	218 (15.8%)	0.282	1.29 (1.07 to 1.56)	**0.009**
Renal impairment	94 (2.4%)	74 (2.9%)	20 (1.4%)	**0.005**	2.36 (1.46 to 4.01)	**0.001**
Ischaemic heart disease	106 (2.7%)	85 (3.3%)	21 (1.5%)	**0.001**	2.77 (1.72 to 4.65)	**<0.001**
Stroke	50 (1.3%)	37 (1.4%)	13 (0.9%)	0.179	1.86 (1.00 to 3.66)	0.059
Family history of myocardial infarction	579 (15.1%)	326 (13.1%)	253 (18.9%)	**<0.001**	0.69 (0.57 to 0.82)	**<0.001**
High waist circumference*	871 (30.9%)	422 (22.3%)	449 (48.1%)	**<0.001**	0.31 (0.26 to 0.37)	**<0.001**
Severe infection	115 (2.9%)	76 (3.0%)	39 (2.8%)	0.779	1.08 (0.73 to 1.61)	0.712
Hepatitis B virus	137 (3.6%)	98 (3.9%)	39 (2.9%)	0.100	1.40 (0.96 to 2.09)	0.087
Hepatitis C virus	48 (1.3%)	31 (1.3%)	17 (1.3%)	0.973	1.08 (0.59 to 2.03)	0.815
Any neoplasm†	86 (2.2%)	60 (2.4%)	26 (1.9%)	0.343	1.51 (0.94 to 2.48)	0.094
Osteoporosis	529 (13.4%)	341 (13.2%)	188 (13.5%)	0.793	1.06 (0.87 to 1.29)	0.568
Spinal fracture	96 (2.4%)	63 (2.5%)	33 (2.4%)	0.895	1.19 (0.78 to 1.85)	0.433
Peripheral non-traumatic fracture	110 (2.8%)	66 (2.6%)	44 (3.2%)	0.267	0.83 (0.57 to 1.23)	0.354
Diverticulitis	59 (1.5%)	34 (1.3%)	25 (1.8%)	0.231	0.84 (0.50 to 1.48)	0.532
Peptic ulcer	424 (10.7%)	270 (10.5%)	154 (11.2%)	0.527	0.97 (0.78 to 1.20)	0.797
Amyloidosis	6 (0.2%)	4 (0.2%)	2 (0.1%)	0.999	1.12 (0.22 to 8.12)	0.895
Vasculitis	11 (0.3%)	5 (0.2%)	6 (0.4%)	0.210	0.48 (0.14 to 1.60)	0.227
Chronic obstructive pulmonary disease	76 (1.9%)	48 (1.9%)	28 (2.0%)	0.740	1.05 (0.66 to 1.71)	0.840
Fibromyalgia‡	535 (13.5%)	265 (10.3%)	271 (19.6%)	**<0.001**	0.47 (0.39 to 0.57)	**<0.001**

The first part of the table (univariate) shows the asbsolute frequencies of each comorbidity in the overall cohort (total), in males and in females, as well as the p value for sex comparison derived from a χ^2 test. The second part displays the results of a comparison between male and female patients after statistical control for age and history of bDMARD use. This section includes the OR for association between sex and the comorbidity presence (female is reference category in the analyses) derived from a logistic regression model, along with their corresponding 95% CIs and p values obtained from Wald tests.
Significant values are marked in bold.
*Waist circumference defined as a categorical variable, with cut-off points based on the general male and female population: ≥102 cm in males; ≥88 cm in females.
†Any neoplasms include: colon cancer, skin melanoma, basocellular carcinoma, lung cancer and lymphoma.
‡Fibromyalgia based on the extreme PRO definition.
bDMARD, biological disease-modifying antirheumatic drug; PRO, patient-reported outcome; SpA, spondyloarthritis.

associated comorbidities with the BASDAI index was FM (4.50 increase, 95% CI 4.34 to 4.67), followed by vasculitis (1.63 increase, 0.22 to 3.03), chronic obstructive pulmonary disease (COPD) (1.16 increase, 0.62 to 1.71) and ischaemic heart disease (1.12 increase, 0.64 to 1.59). In addition, most of the other comorbidities were also significantly associated with a higher BASDAI score, with an increase ranging from 0.49 (peripheral non-traumatic fracture) to 0.87 (severe infection). No significant associations with BASDAI were found for dyslipidaemia, HBV and HBC, history of any neoplasm, spinal fracture, diverticulitis and amyloidosis (figure 1 and online supplemental table S2).

When the ASDAS-CRP index was used as a measure of disease activity, we observed similar trends of association among the studied comorbidities. However, these associations, in general, were weaker and had smaller effect sizes compared with those found for the BASDAI score. For statistically significant comorbidities, these effects ranged from 0.20 (history of myocardial infarction) to 1.50 (FM). Associations with BASDAI found for renal impairment, stroke, peripheral non-traumatic fracture and vasculitis were not statistically significant when evaluated using the ASDAS-CRP (figure 1 and online supplemental table S3).

Notably, the increase in disease activity varied between males and females for certain comorbidities. For instance, this increase was significantly more pronounced in females for high waist circumference (BASDAI: 0.62 for males, 1.05 for females; ASDAS-CRP: 0.27 for males, 0.43 for females) and peptic ulcer (BASDAI: 0.59 for males, 1.11 for females; ASDAS-CRP: 0.09 for males, 0.40 for

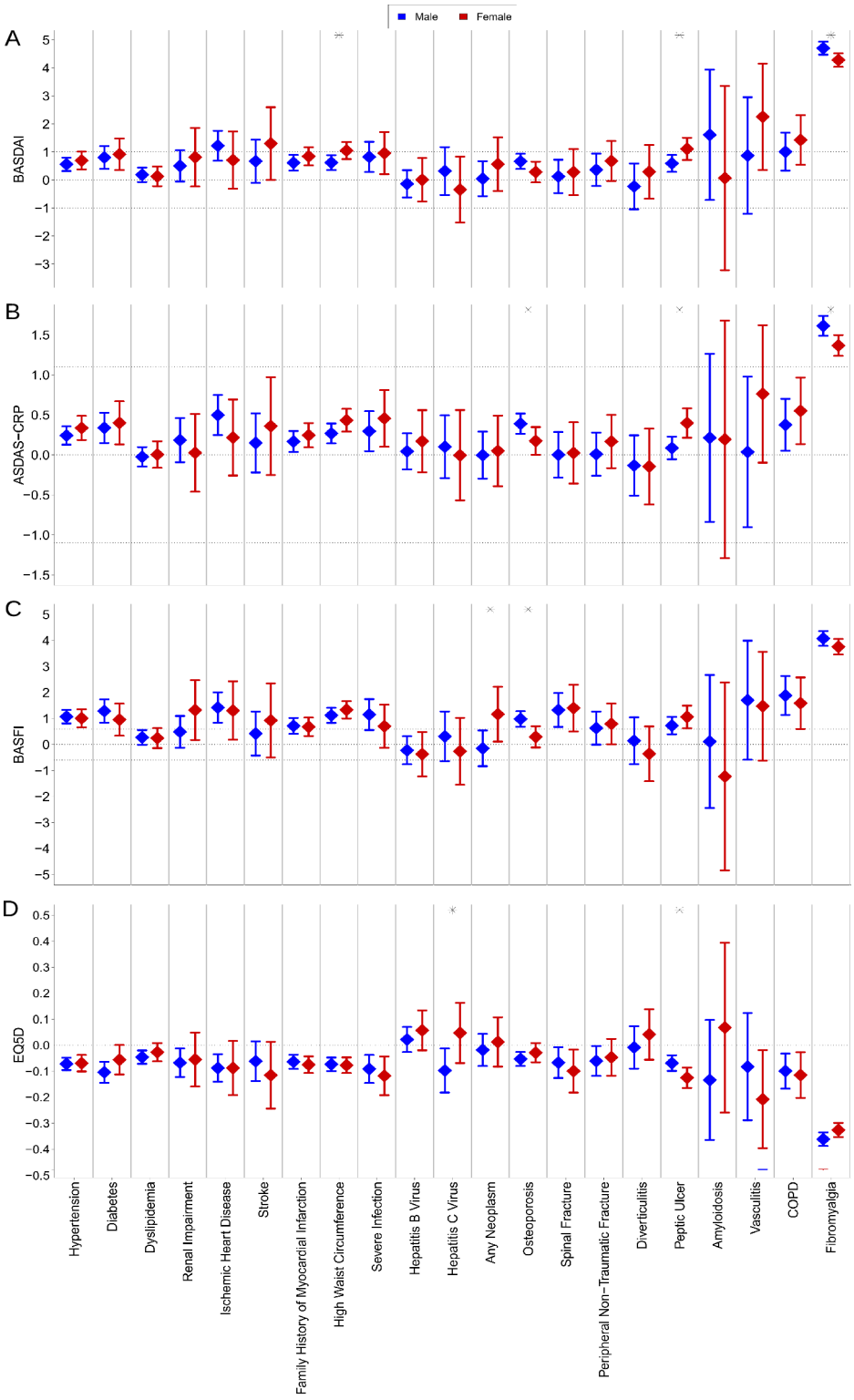

Figure 1 Associations of comorbidities with disease activity, functional ability and life quality in male and female patients with SpA. The figure shows the differences between patients with and without each comorbidity (diamond-shaped points), and their 95% CIs (segments) for male (blue) and female (red) patients with SpA for BASDAI (A), ASDAS-CRP (B), BASFI (C) and EQ5D (D) scores. The asterisks indicate comorbidities with differential association with the score between male and female patients (interaction p value <0.05). ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; COPD, chronic obstructive pulmonary disease; EQ5D, European health-related quality of life questionnaire; SpA, spondyloarthritis.

females). In contrast, FM exhibited a differential effect with a higher impact in male patients (BASDAI: 4.71 for males, 4.28 for females; ASDAS-CRP: 1.61 for males, 1.37 for females). OP also demonstrated a more pronounced effect in males (BASDAI: 0.67 for males, 0.29 for females; ASDAS-CRP: 0.39 for males, 0.17 for females), although the interaction term was not statistically significant in the case of the BASDAI index (p=0.104) (figures 1 and 2, online supplemental table S2 and S3).

Physical function and health-related quality of life

When controlling for age and bDMARD use, BASFI scores were significantly higher in patients with SpA with certain comorbidities, including FM (3.92 increase, 95% CI 3.72 to 4.13), COPD (1.78 increase, 1.18 to 2.37), vasculitis (1.58 increase, 0.04 to 3.12), fractures (0.70 increase, 0.20 to 1.19 for peripheral non-traumatic fracture; 1.35 increase, 0.82 to 1.88 for spinal fracture), history of severe infection (1.00 increase, 0.52 to 1.48), peptic ulcer (0.85 increase, 0.59 to 1.12), OP (0.74 increase, 0.50 to 0.98) and various CV conditions (average increase from 0.26 for dyslipidaemia to 1.40, for ischaemic heart disease) (figures 1 and 2, online supplemental table S4). These associations were consistently found when evaluating comorbidities associations with the EQ5D health-related quality of life score (figures 1 and 3, online supplemental table S5).

The effect of OP on physical function, as measured by the BASFI scale, was of high magnitude and statistically significant in males (0.98 increase, 95% CI 0.68 to 1.28) but not in females (0.29 increase, −0.11 to 0.70). On the other hand, an association with a history of neoplasms was observed only in females (1.17 increase, 0.11 to 2.22), which was not found in male patients with SpA (0.15 decrease, −0.84 to 0.54) (figure 3 and online supplemental table S4).

Regarding the EQ5D index, a substantial decrease in the EQ5D score was observed for females with peptic ulcer (0.125 decrease, 95% CI −0.164 to −0.086) compared with males with the same condition (0.069 decrease, −0.099 to −0.039). In addition, a decrease in health-related quality of life was statistically significant for a history of HCV in males only (0.097 decrease, −0.182 to −0.013). Finally, a more pronounced decrease in health-related quality of life was found in males with FM (0.361 decrease, −0.388 to −0.335) compared with female patients with SpA with this comorbidity (0.326 decrease, −0.353 to −0.299), although the interaction term was not statistically significant in this case (p=0.0663) (figure 3 and online supplemental table S5).

DISCUSSION

Our analysis revealed that, in general, male and female patients with SpA share similar comorbidity profiles, with some noteworthy exceptions that include FM and various CV-related conditions. The presence of comorbidities significantly correlated with higher disease activity scores, decreased physical function and reduced health-related quality of life for both male and female patients. Out of them, FM stood out with a substantial and statistically significant impact on these disease outcomes. Our data reveal significant sex-dependent variations in how comorbidities influence disease activity, physical function and health-related quality of life. Notable examples of these sex-specific impacts include a more pronounced increase in disease activity observed in females with peptic ulcer or high waist circumference compared with male patients with SpA, as well as a greater effect of OP on physical function in male patients.

Our study highlights the significant impact of comorbidities on disease activity assessment in patients with SpA.[1 13] Notably, consistent with previous data,[13] our findings show that the impact of comorbidities on disease activity was clinically significantly lower when assessed using the ASDAS-CRP compared with the BASDAI score. Furthermore, our study observed that the ASDAS-CRP exhibited a lower susceptibility to sex-related influences compared with BASDAI score in the presence of comorbidities. These data highlight the potential benefits of using ASDAS-CRP as the preferred tool for assessing disease activity in patients with SpA, especially when comorbidities are present, to mitigate potential sex-related differences.

Numerous studies and recent meta-analyses have highlighted the increased prevalence of CV comorbidities in axSpA compared with the general population.[1] According to these studies, traditional CV risk factors like dyslipidaemia, hypertension and diabetes tend to affect males and females similarly within the general population, particularly in postmenopausal ages.[5] In our study, though, we observed a higher frequency of CV comorbidities in male patients with SpA compared with their female counterparts, even when the analyses were restricted exclusively to patients aged over 55 years. While the exact reasons behind these sex differences remain unclear, several contributing factors may be at play. Previous research has suggested that male patients with SpA may exhibit a higher prevalence of smoking and physical inactivity compared with females.[1 18] Additionally, studies exploring sex-based disparities in CRP levels have identified consistently elevated baseline levels in male patients compared with female patients.[5 9] These findings emphasise the need for continued investigation into the intricate interplay between sex, SpA and CV health, shedding light on potential areas for targeted interventions and patient care improvements.

On the other hand, our data showed a higher BMI and waist circumference in female patients with SpA compared with male patients with SpA, as well as a notable association between disease activity scores and high waist circumference that was more pronounced in females. These observations align with the results of a prior study, which reported that female patients with axSpA with higher disease activity exhibited a higher percentage of fat and BMI. Conversely, males with elevated disease activity scores tended to have a lower body-fat percentage

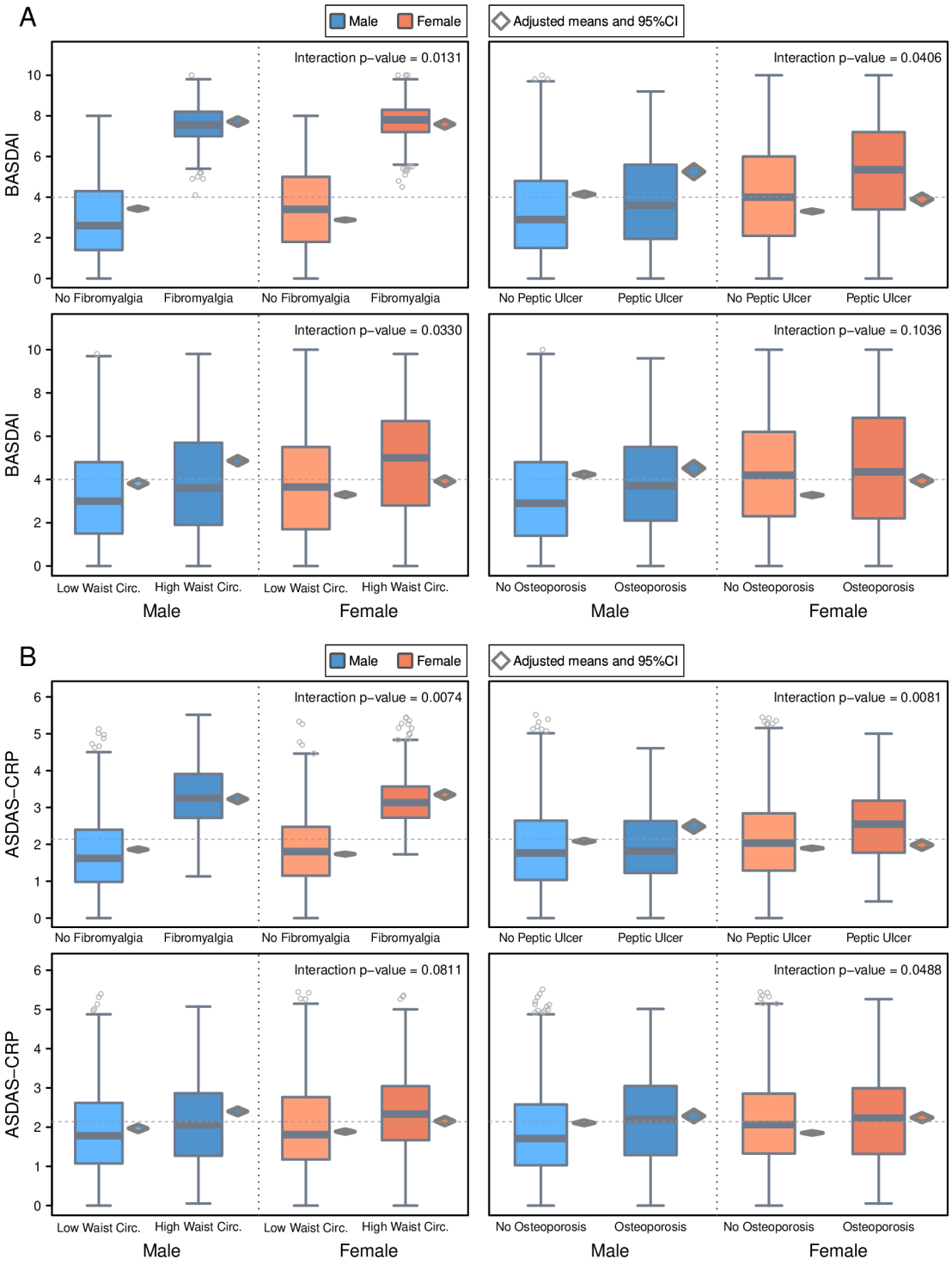

Figure 2 Comorbidities differentially associated with disease activity between male and female patients with SpA. The box plots show the BASDAI (A) and ASDAS-CRP (B) scores for males and females with and without the following comorbidities: fibromyalgia (top-left), peptic ulcer (top-right), high waist circumference (bottom-left) and osteoporosis (bottom-right). The diamond-shaped dots display the adjusted means for each patients' group after statistical control for age and history of biological synthetic disease-modifying antirheumatic drug use, and their extension represent the corresponding 95% CIs. For each panel, the p value for the interaction between sex and the comorbidity is shown in the superior right corner. ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; Circ., circumference; SpA, spondyloarthritis.

and fat mass index.[19] However, further research is needed to better understand the underlying mechanisms driving these associations and to explore potential sex-specific differences in the relationship between high waist circumference and disease activity in SpA, particularly among female patients.

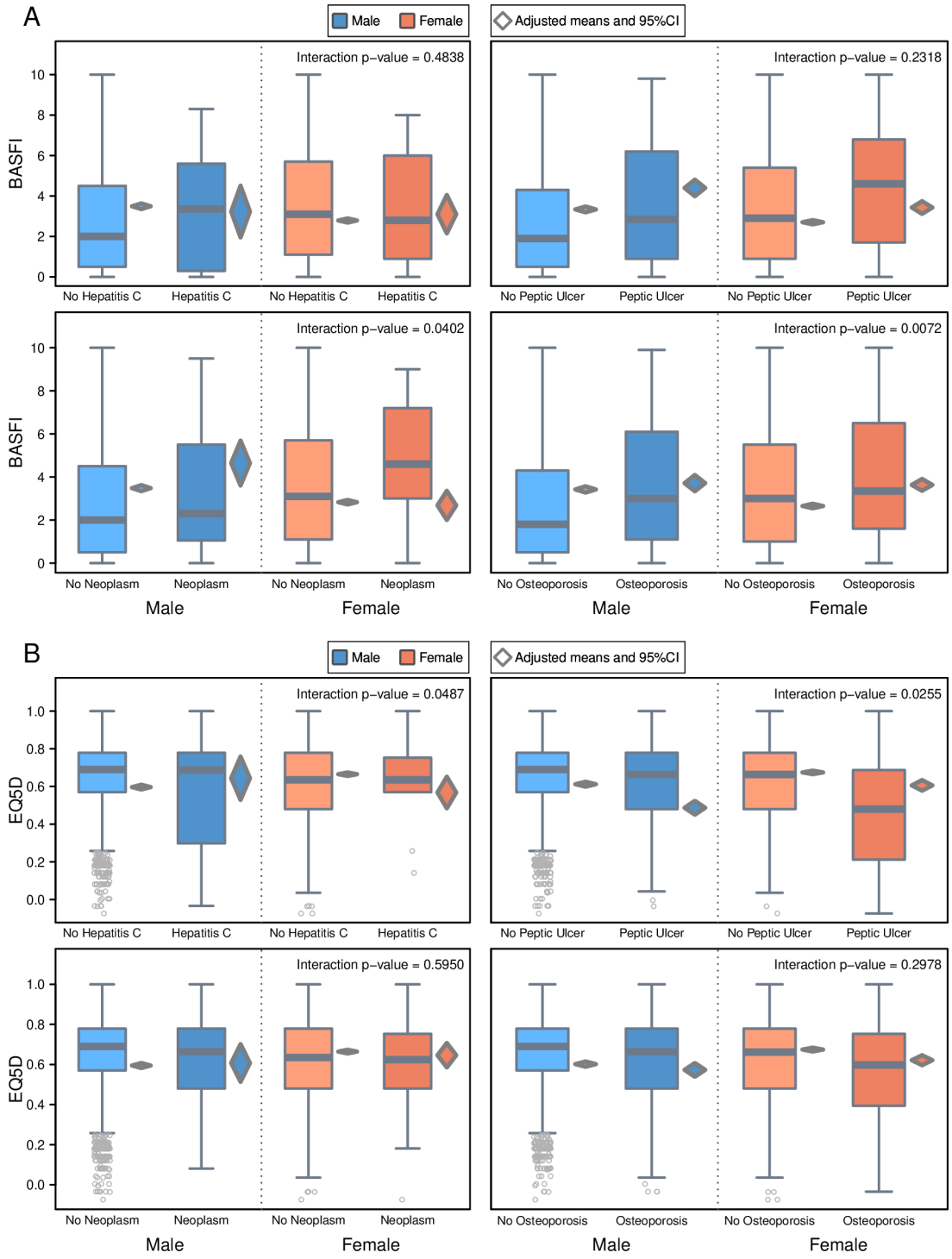

Figure 3 Comorbidities differentially associated with functional ability and life quality between male and female patients with SpA. The box plots show the BASFI (A) and EQ5D (B) scores for males and females with and without the following comorbidities: history of hepatitis C virus infection (top-left), peptic ulcer (top-right), history of neoplasm (bottom-left) and osteoporosis (bottom-right). The diamond-shaped dots display the adjusted means for each patients' group after statistical control for age and history of biological synthetic disease-modifying antirheumatic drug use, and their extension represent the corresponding 95% CIs. For each panel, the p value for the interaction between sex and the comorbidity is shown in the superior right corner. BASFI, Bath Ankylosing Spondylitis Functional Index; EQ5D, European health-related quality of life questionnaire; SpA, spondyloarthritis.

Previous data have reported an unexpectedly high prevalence of OP in young male patients with axSpA.[9 20 21] Additionally, earlier studies have suggested that high disease activity can lead to a higher prevalence of spinal fractures and loss of bone mass in patients with axSpA.[22 23] Our findings align with this previous research, as we observed a higher prevalence of OP (13%) and fractures (2%–3%) than observed in the general population, which was

similar in both male and female patients with SpA within our relatively young population in the COMOSPA study. We also identified in our data an association between OP and disease activity (as measured by the ASDAS-CRP) and worse physical function which was of higher magnitude in male patients compared with female patients.

Of particular interest, peptic ulcers were found to have a higher impact on disease activity in females compared with males in our data. A previous study based on data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis[13] had already reported an association between peptic ulcers and disease activity, which suggested two factors as responsible for this association: first, patients with peptic ulcers might have contraindications for symptomatic control with NSAIDs; second, this association may arise from the long-term requirement for NSAIDs due to active disease. Our results indicate that besides the association with disease activity, peptic ulcers are also associated with health-related quality of life and have a differential impact depending on sex, with a greater impact in females. The reasons for this sex difference cannot be explained with our data, although it might also be related to previous treatment with NSAIDs. However, further research is needed to validate these findings and investigate potential underlying mechanisms of these sex differences.

Regarding the health-related quality of life, it might be worth mentioning an unexpected association found with a history of HCV infection that was only apparent in male patients. To our knowledge, there are no data in the literature regarding this association, which should be interpreted with caution due to the limited number of patients with this comorbidity in our data (n=48, 31 males and 17 females).

Finally, FM is a comorbid condition that typically affects female patients with rheumatic diseases, including SpA. The prevalence of FM in the general population ranges from 2% to 7%, while in patients with axSpA, it has been reported to be more frequent, ranging from 25% to 38%, depending on the criteria used.[24] It is worth noting that patients with SpA with concurrent FM often report significantly worse disease activity, as assessed by the BASDAI, as well as impaired physical function, higher global severity scores and poorer health-related quality of life.[25 26] In our study, we observed a prevalence of FM in 19.6% of female patients with SpA and 10.3% of male patients using the extreme PRO definition,[12] as well as a strong association with a higher disease activity and physical function, and a lower health-related quality of life. Surprisingly, our findings reveal that FM has a slightly higher impact on disease activity in males compared with females, with a greater mean difference in the BASDAI index than for ASDAS-CRP score. At this point, it is important to acknowledge a significant limitation of our study: the COMOSPA study did not encompass specific criteria for identifying the presence of FM. Consequently, we subsequently categorised patients with FM comorbidity according to the extreme PRO definition, which has been previously employed in other studies.[12] This definition is dependent on the BASDAI score. Consequently, its correlation with disease activity, as measured by both the BASDAI and, to a lesser extent, the ASDAS-CRP score, may be potentially artifactitious, owing to a potential confounding effect. These findings align with previous research,[24 25] highlight a potential impact of FM on disease activity in patients with SpA and suggest a novel sex-specific aspect of this association. Nevertheless, the use of the extreme PRO definition for FM classification underscores the need for additional research to validate these findings using alternative FM criteria.

Further limitations of our study include that our data are derived from a cross-sectional analysis, which limits our ability to establish causal relationships between comorbidities and disease activity and severity. In this regard, longitudinal studies are necessary to explore the temporal associations between these variables. A key strength of this study, however, is its large sample size from a broad range of countries worldwide.

In summary, the sex-related variations in comorbidities and their influence on disease activity among patients with SpA emphasise the significance of accounting for sex-specific comorbidity profiles in the management and treatment of this population. Our study underscores the importance of employing the ASDAS-CRP when comorbidities are present, as it helps mitigate sex-related disparities in disease assessment.

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