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ORIGINAL ARTICLE

Real-life data on the comorbidities in spondyloarthritis from our multicenter nationwide registry: BioStar

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ABSTRACT

Objectives: Considering that the comorbid situations during the management of Spondyloarthritis (SpA) have been underlined in several recommendations, the main objective of this study was to evaluate the comorbid conditions of Turkish patients with SpA.

Patients and methods: This cross-sectional observational study was conducted with 1,242 SpA patients (844 males, 398 females; mean age: 43.9±11.0 years; range, 19 to 81 years) diagnosed according to the modified New York criteria for ankylosing spondylitis or the Assessment of SpondyloArthritis International Society (ASAS) criteria. The patient data were collected from the Biologic and targeted Synthetic antirheumatic drugs Registry (BioStar) between February 1, 2019, and December 29, 2020. Clinical and demographic data, including, age, sex, disease duration, body mass index (BMI), pain, patient's global assessment, physician's global assessment, Bath Ankylosing Spondylitis Disease Activity Index, Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Metrology Index, and Maastricht Enthesitis Score, were recorded. Comorbid conditions were recorded by filling out a questionnaire according to the clinical history or medical records. Charlson Comorbidity Index and Rheumatic Disease Comorbidity Index scores were calculated from the gathered comorbidity information.

Results: Nine hundred thirteen patients had radiographic axial SpA, 153 had nonradiographic axial SpA, and 176 had peripheral SpA. The most common comorbidities were hypertension (HT) (n=167, 13.4%), diabetes mellitus (DM) (n=83, 6.7%), thyroid disorders (n=64, 5.6%), and depression (n=61, 4.9%). The comorbidities and the calculated comorbidity indices were significantly higher in females, in those with a BMI >25 kg/m^2, and those over 60 years of age. No relationship was found between smoking and alcohol use and comorbidities. A significantly higher prevalence of HT and DM in peripheral SpA patients and a lower prevalence of thyroid disorders in radiographic axial SpA patients were observed.

Conclusion: The most commonly reported comorbidities were HT, DM, thyroid disorders, and depression in SpA patients according to the BioStar database. The frequency of comorbidities and composite comorbidity scores were higher among females, older (>60 years) patients, and overweight (BMI >25 kg/m^2) patients.

Keywords: Charlson Comorbidity Index, comorbidities, Rheumatic Disease Comorbidity Index, Spondyloarthritis, BioStar.

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Spondyloarthritis (SpA) is a group of chronic, inflammatory musculoskeletal diseases that may also display extraarticular manifestations. Ankylosing spondylitis (AS), psoriatic arthritis, and inflammatory bowel disease-associated arthritis are among this group. In recent years, the definition of the disease was rewritten by considering the earlier forms, which have no radiographically evident features but with inflammatory signs detected by magnetic resonance imaging in the concept of the Assessment of SpondyloArthritis International Society (ASAS) definition.[1] According to the ASAS definition, SpA is classified as axial-dominant SpA and peripheral arthritis-dominant SpA. The former category is made up of radiographic axial SpA (AxSpa) and nonradiographic (nr)-AxSpA. The peripheral arthritis-dominant SpA group consists of psoriatic arthritis, reactive arthritis, inflammatory bowel disease-associated arthritis, and undefined SpA. These diseases carry a significant health-related and socioeconomic burden on patients and communities.

Comorbidity is defined as the presence of more than one disease or condition with varying pathogenesis in the same person at the same time by the Centers for Disease Control and Prevention.[2] Comorbid conditions increase the morbidity and mortality of the primary disease and decrease the outcome measure scores and functionality of patients. Additionally, the presence of comorbid conditions with SpA may decrease the tolerability of medications and indeed may influence the decision to use biological drugs.[3] The extraarticular manifestations and comorbidities of SpA patients were found to increase disability and healthcare expenditures.[4] The association of SpA with comorbid situations were previously evaluated.[5-8] Some of the recommendations/guidelines underline the importance of considering comorbid situations during the management of SpA.[9,10] The main objective of this study was to evaluate the comorbid conditions of Turkish patients with SpA.

PATIENTS AND METHODS

This cross-sectional observational study was conducted with 1,242 patients (844 males, 398 females; mean age: 43.9±11.0 years; range, 19 to 81 years) at thirteen rheumatology and/or physical medicine departments, most of which are tertiary or academic instutions, in different cities of Türkiye. Data collection was performed from the Biologic and targeted Synthetic antirheumatic drugs Registry (BioStar) database between February 1, 2019, and December 29, 2020. Eligible subjects were chosen among patients with a diagnosis of SpA according to either the modified New York criteria for AS or the ASAS criteria.[1] Patients unable to fill out questionnaires were excluded. Clinical and demographic data, including, age, sex, disease duration, were recorded. The body mass index (BMI) was calculated according to the predetermined formula [weight (kg)/square of height (m^2)]. A BMI >25 kg/m^2 was accepted as the cut-off value defining overweight patients. Patients with radiologically proven sacroiliitis on x-rays were considered AxSpA. Patients without radiographical changes on the pelvis x-ray were considered nr-AxSpA. If the axial pattern was the dominant feature, they were defined as predominantly axial nr-SpA (Ax-nr-SpA), and subjects with predominantly peripheral articular features were classified as predominantly peripheral SpA (p-SpA).

The Visual Analog Scale for pain, patient's global assessment (PGA), physician's global assessment (PhyGA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-reactive protein (CRP), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) were recorded. The CRP and erythrocyte sedimentation rate were obtained to be used for calculation of disease activity measures. Data about the history of SpA treatment were gathered.

Comorbid conditions of subjects were recorded by filling out a questionnaire with closed questions according to the clinical history or, if present, medical records. Any report provided by the patient or obtained from medical records in favor of the presence of any condition was taken into consideration. The questionnaire contains questions about hypertension (HT), diabetes mellitus (DM) (including any complication related to DM), renal disease, chronic lung diseases (asthma or chronic obstructive pulmonary disease), pulmonary

circulation disorders, thyroid dysfunction (hypo- or hyperthyroidism, any thyroid surgery, and consuming thyroid hormone replacement or suppressing medicine), cardiovascular system disorders (coronary artery disease, myocardial infarction, congestive heart failure, peripheral vascular events, and cardiac valve disease) gastrointestinal (GI) system disorders (peptic ulcer and GI bleeding), hepatic disorders, history of cancer, neurologic disorders (stroke, dementia, atlantoaxial instability, and spinal cord injury/cauda equina syndrome), psychiatric disorders (depression/psychosis). Serologic tests for viral hepatic diseases and human immunodeficiency virus were recorded. Charlson Comorbidity Index (CCI)[11] and Rheumatic Disease Comorbidity Index (RDCI)[12] scores were calculated from the gathered comorbidity information.

The comparison of comorbid conditions and comorbidity indices was performed according to the sex difference, disease subgroups, age, being overweight, alcohol consumption (consumers *vs.* nonconsumers), and smoking habit (smokers *vs.* nonsmokers). Although the general trend to define elderly individuals is accepted as 65 years of age, the comparison of subjects was performed by defining the cut-off age at 60 years as the number of subjects over 65 years was insufficient for statistical comparison. The alcohol-consuming and smoking status were defined based on subject's answer. Subjects who consumed alcohol and smoked in any time of life were defined as alcohol-consumers and smokers respectively.

Statistical analysis

Data were analyzed using R version 4.0.4 software (America, Lucent Technologies Inc., NJ, USA). All categorical variables were summarized with frequencies and percentages, whereas the numerical variables were expressed as mean ± standard deviation (SD). The numerical variables were compared across two groups with the Mann-Whitney U test or the independent samples t-test. Three or more groups were compared by the Kruskal-Wallis test or analysis of variance (ANOVA) depending on their distribution. Significant results from the Kruskal-Wallis test and ANOVA were followed by post hoc tests, and Bonferroni-corrected p values were calculated. The assumption of normality was assessed with the Shapiro-Wilk test in addition to visual inspections of quantile-quantile (QQ) and probability-probability (PP) plots. The homogeneity of variance was assessed using Levene's test. The Spearman correlation coefficient was calculated to measure the relationship between two numerical variables. The chi-square test was used to test the associations between two categorical variables. A chi-square post hoc test (the chisq.posthoc.test package) was applied to the significant associations, and the Bonferroni adjusted *p* values were calculated. A *p* value of <0.05 was considered statistically significant.

RESULTS

The mean age of females was significantly higher than males in the study (46.4±11.0 *vs.* 42.8±10.7 years, $p<0.001$). The mean duration of disease for all subjects was 112.3±88.6 months. The mean duration of disease was longer in males than in females (120.5±93.6 *vs.* 94.8±73.8 months, $p<0.001$). The rate of alcohol consumption (13.9% *vs.* 2.6%, $p<0.001$) and smoking (%63.3 *vs.* 28.8, $p<0.001$) were significantly higher in males than in females. The mean BMI of females was significantly higher compared to males (28.6±5.3 *vs.* 26.8±4.1 kg/m^2, $p<0.001$). Similarly, the rate of females with a BMI >25 was higher (71.5% *vs.* 64.7%, $p=0.017$, Table 1).

The subjects were subdivided into three subgroups according to the type of SpA: the AxSpA group (n=913), the Ax-nr-SpA group (n=153), and the p-SpA group (n=176). There was a male predominance in all subgroups, with the highest value in the AxSpA group (72.5%). The mean age was highest in the p-SpA subgroup (47.0±11.8 years). The shortest duration of disease was in the Ax-nr-SpA subgroup (81.7±63.7 months). The other demographic characteristics are shown in Tables 1 and 2.

The most frequently reported comorbid conditions were HT (n=167, 13.4%), DM (n=83, 6.7%), and thyroid dysfunction (n=64, 5.6%; Figure 1). Assessment of these conditions according to sexes revealed that HT (17.3% *vs.* 11.6%, $p=0.006$), thyroid dysfunction (12.6% *vs.* 2.3%, $p<0.001$), DM (10.1% *vs.* 5.1%, $p= 0.001$), and depression (7.5% *vs.* 3.7%, $p=0.003$) were

significantly higher among females than males (Table 1).

When disease subgroups were considered, HT (19.9%, p=0.023) and DM (11.4%, p=0.026) were statistically higher in the p-SpA subgroup than in the other two subgroups. Thyroid dysfunction was the lowest in the AxSpA subgroup (4.2%, p=0.004). There were no cases of liver disease or acquired immunodeficiency syndrome (AIDS). Only two cases of congestive heart failure (both in the p-SpA group; 1.1%, p=0.002) and one case of dementia were reported.

Hypertension (55.9% *vs.* 10.0%, p<0.001), DM (28.0% *vs.* 5.0%, <0.001), thyroid dysfunction (10.5% *vs.* 5.2%, p=0.039), and renal disease (6.5% *vs.* 1.4, p<0.001) were significantly higher among older (>60 years) patients (Table 3).

The distribution of comorbid conditions according to predetermined BMI level revealed a similar pattern to those defined according to age. Hypertension, DM, and thyroid dysfunction were significantly higher in overweight (BMI>25 kg/m^2) patients (Table 3).

Table 1. Comparison of sexes by demographic and frequencies of comorbid conditions

	Male (n=844)			Female (n=398)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Demographic characteristics							
Age (year)			42.8±10.7			46.4±11.0	**<0.001**
Disease duration (month)			120.5±93.6			94.8±73.8	**<0.001**
Smokers	529	63.3		114	28.8		**<0.001**
Alcohol consumers	110	13.9		10	2.6		**<0.001**
BMI	26.8	4.1		28.6	5.3		**<0.001**
BMI >25	545	64.7		284	71.5		**0.017**
Comorbid conditions							
Hypertension	98	11.6		69	17.3		**0.006**
Thyroid dysfunction	18	2.3		46	12.6		**<0.001**
Diabetes mellitus	43	5.1		40	10.1		**0.001**
Depression	31	3.7		30	7.5		**0.003**
Peptic ulcer	29	3.4		18	4.5		0.349
Chronic lung disease	21	2.5		16	4.0		0.138
Cardiovascular diseases	38	4.5		9	2.3		0.053
Kidney disease	16	1.9		6	1.5		0.628
Complicated diabetes mellitus	7	0.8		5	1.3		0.473
Malignancy	4	0.5		3	0.8		0.539
Cerebrovascular disease	3	0.4		1	0.3		0.762
Gastrointestinal bleeding	7	0.8		1	0.3		0.235
Myocardial infarction	12	1.4		1	0.3		0.059
Congestive heart failure	1	0.1		1	0.3		0.586
Peripheral vascular disease	4	0.5		1	0.3		0.563
Hemiparesis	3	0.4		1	0.3		0.762

SD: Standard deviation; BMI: Body mass index.

Table 2. Comparison of disease subgroups by demographic features and of comorbid conditions

	Axial radiographic SpA (n=913)			Axial non-radiographic SpA (n=153)			Peripheral SpA (n=176)			Total (n=1,242)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Demographic characteristics													
Males	662a	72.5		91[a]	59.5		91[b]	51.7		844	68.0		**<0.001**
Age mean (year)			44.0±10.8[a]	40.1[b]	9.9	40.1±9.9[b]			47.0±11.8[c]			43.9±11.0	**<0.001**
Married	757	82.9		119	77.8		152	86.4		1028	82.8		**0.118**
Disease duration (month)			118.4± 92.3[a]			81.7±63.5[b]			107.1±81.5[a]			112.3±88.6	**<0.001**
Smokers	503[a]	55.6		65[b]	43.0		75[b]	42.6		643	52.2		**<0.001**
Alcohol-consumers	97	11.3		10	6.7		13	7.7		120	10.2		0.117
BMI			27.4±4.4			26.9±4.5			27.8±5.3			27.4±4.6	0.443
BMI >25	611	67.1		102	66.7		116	66.3		829	66.9		0.978
Comorbid conditions													
Hypertension	115[a]	12.6		17[a]	11.1		35[b]	19.9		167	13.4		**0.023**
Diabetes mellitus	55[a]	6.0		8[a]	5.2		20[b]	11.4		83	6.7		**0.026**
Thyroid dysfunction	36[a]	4.2		13[b]	9.8		15[b]	8.8		64	5.6		**0.004**
Depression	43	4.7		8	5.2		10	5.7		61	4.9		0.845
Cardiovascular disease	35	3.8		3	2.0		9	5.1		47	3.8		0.323
Peptic ulcer	36	3.9		3	2.0		8	4.5		47	3.8		0.419
Chronic lung disease	26	2.8		7	4.6		4	2.3		37	3.0		0.426
Kidney disease	17	1.9		1	0.7		4	2.3		22	1.8		0.498
Myocardial infarction	9	1.0		0	0.0		4	2.3		13	1.0		0.122
Complicated DM	6	0.7		2	1.3		4	2.3		12	1.0		0.120
Malignancy	5	0.5		1	0.7		1	0.6		7	0.6		0.987
GI bleeding	6	0.7		0	0.0		2	1.1		8	0.6		0.436
Peripheral vascular disease	5	0.5		0	0.0		0	0.0		5	0.4		0.405
Cerebrovascular disease	3	0.3		0	0.0		1	0.6		4	0.3		0.661
Hemiparesis	2	0.2		0	0.0		2	1.1		4	0.3		0.109
Congestive heart failure	0[a]	0.0		0[a]	0.0		2[b]	1.1		2	0.2		**0.002**
RDCI			0.4±0.8			0.4±0.8			0.5±1.1			0.4±0.8	0.261
CCI			0.2±0.6			0.2±0.6			0.4±1.6			0.2±0.8	0.311

SD: Standard deviation; BMI: Body mass index; a, b, c: The groups which were marked by different letters have significant difference than the other groups in the identical parameter according to Bonferroni post-hoc analysis; DM: Diabetes mellitus; GI: Gastrointestinal; RDCI: Rheumatic Disease Comorbidity Index; CCI: Charlson Comorbidity Index.

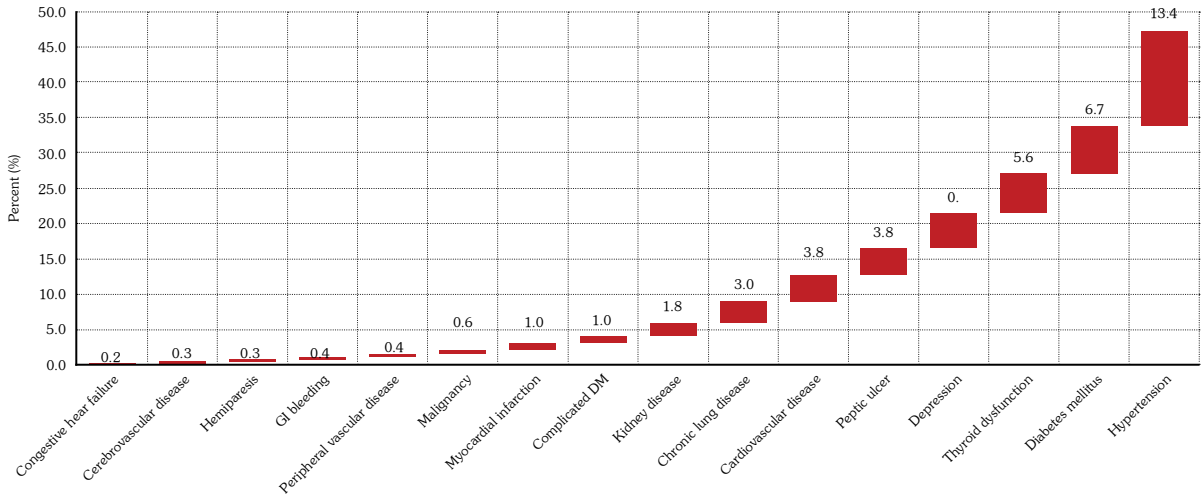


Figure 1. Frequency of each comorbid condition by considering the study population as a whole.

The CCI scores were compared according to differently classified groups of subjects. The mean RDCI scores were significantly higher in females than in males (0.5±0.9 *vs.* 0.4±0.8, p<0.001), in patients with a BMI score >25 kg/m^2 compared to those with BMI scores ≤25 kg/m^2 (0.5±0.9 *vs.* 0.3±0.8, p<0.001), and in older patients compared to younger individuals (1.2±1.1 *vs.* 0.4±0.8, p<0.001). A similar trend was observed for the CCI (Figures 2 and 3). Smoking and alcohol consumption did not create any significant difference in comorbidity indices (Table 4). The composite comorbidity score assessment among various disease phenotypes revealed no significant difference (Table 2). The correlation between these two comorbidity scores was relatively strong (r=0.731, p<0.001).

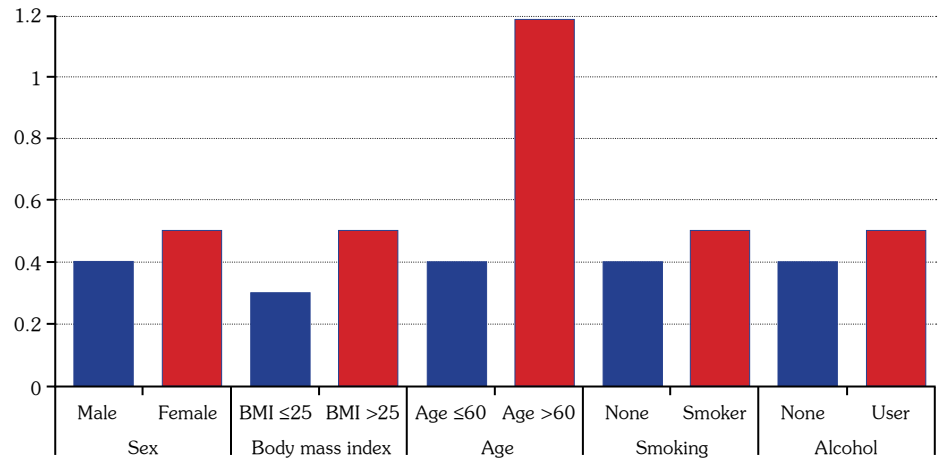
According to CCI values, the scores were categorized as mild (1-2), moderate (3-4), and severe (≥5).[13] For RDCI, there was no predefined value for such a categorization. In a study performed on rheumatoid arthritis patients, a cut-off value of 2 was determined for RDCI for severity analysis.[14] In our study, we categorized the patients by using CCI scores ≥3 and by using RDCI scores ≥2 as having moderate to severe comorbidity. The ratio of patients with moderate to severe comorbidity was 1.85% (n=23) and 11.03% (n=137) according to CCI and RDCI scores, respectively. The mean age of patients with a CCI score ≥3 was higher than those with a CCI score <3 (55.4±10.5 *vs.* 43.7±10.9 years, p<0.001). According to categories of patients by RDCI, patients with a lower comorbidity burden (RDCI <2) were younger than those with a higher comorbidity score category (42.9±10.5 *vs.* 52.8±10.7 years, p<0.001). There was no significant difference in having a CCI score ≥3 among the sexes. In contrast, the ratio of females with a RDCI score ≥2 was higher compared to males (14.3% *vs.* 9.5%, p=0.006). The mean BMI of patients with a higher RDCI category was higher than in the category with lower scores (29.7±5.3 *vs.* 27.1±4.4, p<0.001). Although the number of patients with a CCI score ≥3 was relatively small (n=23), a similar pattern in the mean BMI values was also observed in this group (30.4±4.8 in patients with a CCI score ≥3 *vs.* 27.3±4.5 in patients with a CCI score <3, p=0.003). A statistically higher percentage of overweight patients had a RDCI score ≥2 compared to those with a BMI ≤25 (12.6% *vs.* 7.6%, p=0.006). The Pearson chi-square test with Yates' continuity correction test showed no significant association between BMI and CCI (p=0.066).

Among disease subgroups, the percentage of being RDCI ≥2 was 10.5%, 9.2%, and 15.3% for AxSpa, nr-AxSpA, and p-Spa, respectively (p=0.127). The percentage of AxSpA patients with a CCI score ≥3 was 1.5%. The same figures were 2% and 3.4% for nr-AxSpa and p-Spa subgroups, respectively (p=0.238).

Table 3. Comparison of comorbid conditions according to 60 years of age and BMI of 25 kg/m^2 as the cut-off points

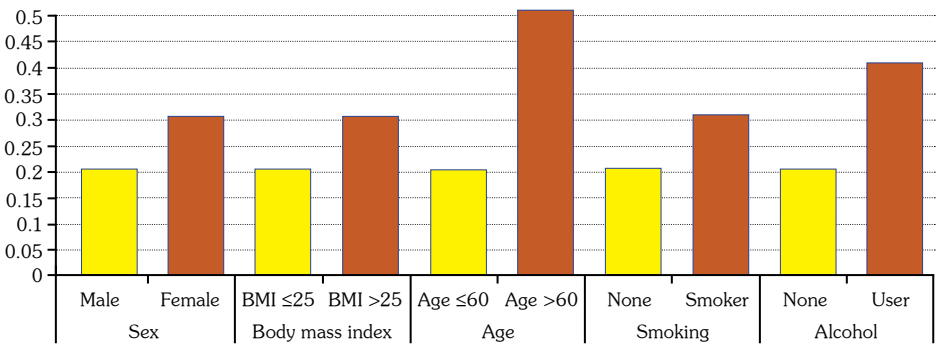
	Age					Body Mass Index				
	≤60 years (n=1149)		>60 years (n=93)			≤25 kg/m^2 (n=407)		>25 kg/m^2 (n=832)		
	n	%	n	%	*p*	n	%	n	%	*p*
Hypertension	115	10.0	52	55.9	**<0.001**	25	6.1	142	17.1	**<0.001**
Diabetes mellitus	57	5.0	26	28.0	**<0.001**	9	2.2	73	8.8	**<0.001**
Thyroid dysfunction	55	5.2	9	10.5	**0.039**	13	3.5	51	6.5	**0.037**
Depression	53	4.6	8	8.6	0.087	22	5.4	39	4.7	0.583
Cardiovascular diseases	40	3.5	7	7.5	0.05	14	3.4	33	4.0	0.649
Kidney disease	16	1.4	6	6.5	**<0.001**	5	1.2	17	2.0	0.308
Chronic lung disease	32	2.8	5	5.4	0.157	7	1.7	30	3.6	0.067
Peptic ulcer	45	3.9	2	2.2	0.391	19	4.7	28	3.4	0.260
Gastrointestinal bleeding	6	0.5	2	2.2	0.059	4	1.0	4	0.5	0.300
Myocardial infarction	11	1.0	2	2.2	0.277	4	1.0	9	1.1	0.872
Peripheral vascular disease	4	0.3	1	1.1	0.287	2	0.5	3	0.4	0.733
Complicated diabetes mellitus	11	1.0	1	1.1	0.911	1	0.2	11	1.3	0.069
Cerebrovascular disease	4	0.3	0	0.0	0.569	2	0.5	2	0.2	0.464
Malignancy	7	0.6	0	0.0	0.450	2	0.5	5	0.6	0.809
Congestive heart failure	2	0.2	0	0.0	0.687	1	0.2	1	0.1	0.605
Dementia	1	0.1	0	0.0	0.776	0	0.0	1	0.1	0.484
Hemiparesis	4	0.3	0	0.0	0.569	2	0.5	2	0.2	0.464

BMI: Body mass index.



Rheumatic Disease Comorbidity Index	0.4	0.5	0.3	0.5	0.4	1.2	0.4	0.5	0.4	0.5

Figure 2. Comparison of RDCI scores according to predefined groups.
RDCI: Rheumatic Disease Comorbidity Index.



Charlson Comorbidity Index	0.2	0.3	0.2	0.3	0.2	0.5	0.2	0.3	0.2	0.4

Figure 3. Comparison of CCI scores according to predefined groups.
CCI: Charlson Comorbidity Index.

We assessed if there was any significant correlation between patient-reported outcome measures (PROMs) and comorbidity indices to analyze the relationship between disease and comorbidity status. The correlation coefficients, although some of them statistically significant, reflected a weak relationship. Assessments were separately performed within each disease group. In the AxSpA group, the RDCI scores were significantly correlated with the BASMI (r=0.110, p=0.009), MASES (r=0.100, p=0.020), BASFI (r=0.083, p=0.023), and pain assessment scores (Visual Analog Scale; r=0.66, p=0.047). The CCI scores demonstrated statistically significant correlation with BASFI scores in this group (r=0.085, p=0.011). In the Ax-nr-SpA group, only PGA (r=0.254, p=0.0017) and PhyGA (r=0.180, p=0.028) scores were significantly correlated with CCI scores. In the p-SpA subgroup, RDCI was positively correlated with BASMI (r=0.199, p=0.008), MASES (r=0.279, p=0.007), ASDAS-CRP (r=0.194, p=0.01), and BASFI (r=0.179, p=0.03). The correlations of PROM with CCI in the last subgroup were as follows: MASES (r=0.297, p=0.004), BASDAI (r=0.219, p=0.006), ASDAS-CRP (r=0.254, p=0.001), and BASFI

Table 4. Comparison of comorbidity index scores among differently categorized groups of subjects

	Male (n=844)	Female (n=398)	*p*
Rheumatic Disease Comorbidity Index	0.4±0.8	0.5±0.9	**<0.001**
Charlson Comorbidity Index	0.2±0.9	0.3±0.7	**0.030**
	BMI ≤25 (n=410)	BMI >25 (n=829)	
Rheumatic Disease Comorbidity Index	0.3±0.8	0.5±0.9	**<0.001**
Charlson Comorbidity Index	0.2±1.0	0.3±0.7	**0.002**
	Age ≤60 (n=1149)	Age >60 (n=93)	
Rheumatic Disease Comorbidity Index	0.4±0.8	1.2±1.1	**<0.001**
Charlson Comorbidity Index	0.2±0.8	0.5±0.9	**<0.001**
	Non-smokers (n=589)	Smokers (n=643)	
Rheumatic Disease Comorbidity Index	0.4±0.8	0.5±0.9	0.277
Charlson Comorbidity Index	0.2±0.6	0.3±1.0	0.450
	Alcohol-nonconsumers (n=1056)	Alcohol-consumers (n=120)	
Rheumatic Disease Comorbidity Index	0.4±0.8	0.5±1.1	0.803
Charlson Comorbidity Index	0.2±0.6	0.4±1.8	0.603

SD: Standart deviation; BMI: Body Mass Index.

Table 5. Correlations of comorbidity indices with PROMs, disease activity measures, and metrology indices

	Axial (radiographic) SpA		Predominantly axial nr-SpA		Predominantly peripheral nr-SpA	
	r	*p*	r	*p*	r	*p*
Rheumatic Disease Comorbidity Index						
BASMI	0.110	**0.0009**	-0.146	0.074	0.199	**0.008**
MASES	0.100	**0.020**	0.108	0.230	0.279	**0.007**
BASDAI	0.044	0.206	0.147	0.093	0.157	0.05
ASDAS-CRP	0.031	0.357	0.131	0.118	0.194	**0.01**
BASFI	0.083	**0.023**	0.041	0.686	0.179	**0.03**
Patient global assessment	0.025	0.464	0.212	0.0095	0.003	0.970
Physician global assessment	0.014	0.668	0.075	0.358	0.064	0.406
Pain	0.066	0.047	0.092	0.264	0.085	0.272
Fatigue	0.047	0.162	0.145	0.076	0.072	0.352
Charlson Comorbidity Index						
BASMI	0.085	**0.011**	-0.038	0.642	0.131	0.09
MASES	0.075	0.082	0.152	0.091	0.297	**0.004**
BASDAI	-0.003	0.924	0.067	0.446	0.219	**0.006**
ASDAS-CRP	0.064	0.059	0.159	0.055	0.254	**0.001**
BASFI	0.079	**0.031**	0.189	0.062	0.202	**0.02**
Patient global assessment	0.038	0.252	0.254	**0.0017**	0.085	0.270
Physician global assessment	0.028	0.402	0.180	**0.028**	0.151	**0.049**
Pain	0.048	0.150	0.071	0.386	0.151	0.05
Fatigue	0.032	0.335	0.129	0.117	0.211	**0.006**

BASMI: Bath Ankylosing Spondylitis Metrology Index; MASESS: Maastricht Ankylosing Spondylitis Enthesitis Score; BASDAI: Bath Ankylosing Spondylitis Disease Acticity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; BASFI: Bath Ankylosing. Funcitonal Index

(r=0.202, p=0.02). The patient-reported fatigue score was also positively correlated with CCI (r=0.211, p=0.006, Table 5).

DISCUSSION

Comorbid conditions are considered the main factors in the management of various diseases. The presence of any comorbidity may influence the outcome of a given treatment and may worsen the expected side-effect profile. Each comorbidity is considered a burdensome factor, both medically and financially. Many of the guidelines/recommendations advise that comorbidities should not be ignored in the management of SpA.[9,10]

Biologic and targeted Synthetic antirheumatic drugs Registry (BioStar) is a nation-wide, web-based project of Turkish League Against Rheumatism (TLAR). The aim of the project is to gather the clinical information about Turkish patients with inflammatory rheumatic diseases who are under treatment of biologic disease-modifying antirheumatic drugs (bDMARDs). One of the main parts of the project is concerning SpA.

In this cross-sectional investigation, the most frequently reported comorbidity was HT (13.4%), with a frequency of 17.3% among females, 19.9% among patients with p-SpA, and 55.9% among older (>60 years) individuals. Hypertension was reported as the most frequent (19% and 52%) comorbidity in AxSpA patients in two recent trials.[15,16] In the ASAS-COMOSPA trial, HT was considered a risk factor for cardiovascular diseases, and its mean frequency was 33.5% (95% CI 32.0 to 35.0), with a significant geographical variation (e.g., 60% in Northern European countries).[5] In a cohort trial from Taiwan, HT prevalence was compared among AS and non-AS groups, which was found 24% for each group.[17] Hypertension was found to be related to disease duration (odds ratio=1.129 for each five-year increase in duration of SpA), age, male sex, high BMI, and use of corticosteroids or DMARDs.[18] In our study, HT frequency was also higher among older patients (55.6%) and overweight subjects (17.1%). Furthermore, HT was more frequent among females and patients with p-SpA (17.3% and 19.9%, respectively). The mean age of females in our participants and of p-SpA patients were higher than their counterpart groups. Age is potentially a significant factor for the higher frequency of HT among mentioned groups. In contrast to our results, the AxSpA group was found to be the most frequently encountered disease grou to H.[18] The risk of developing HT is known to increase with the use of glucocorticoids. The p-SpA group in our trial was composed mainly of psoriatic arthritis and inflammatory bowel disease-related arthritis patients (data not shown). The consumption of NSAIDs (nonsteroidal anti-inflammatory drugs) and glucocorticoids are generally more frequent in these diseases. This may be one of the reasons why HT was higher in this group.

In the ASAS-COMOSPA study, similar to HT, DM was also considered a cardiovascular risk factor.[5] Its prevalence among 3,984 patients was 8.8%. The risk of AS patients for type 2 DM was found to be 17.4% higher than the general population in Taiwan. Additionally, females in the AS cohort had a higher incidence of type 2 DM than males in the same cohort. Diabetes mellitus incidence increased by progressive age in the AS and non-AS cohorts. However, younger AS patients, particularly those suffering from other comorbidities, have a higher relative risk of developing DM than the normal population with a similar age.[17] In a recent trial, insulin resistance measurement of nondiabetic SpA patients were higher than controls. In this analysis, HLA-B27 status and disease duration were independently associated with a higher homeostasis model assessment (HOMA)-2 index.[19] In our study, DM was the second most frequent comorbidity (6.7%). It was higher in patients with p-SpA (11.4%), in females (10.1%), and in older subjects (28.0%). In our trial, DM frequency in overweight patients was higher than in nonoverweight patients (8.8% *vs.* 2.2%). In contrast to the relatively higher percentage of DM, complicated DM (e.g., DM-related vasculopathy, renal failure, neuropathy, and hospitalization) was about 1%. Association of DM with SpA is considered a result of combined effects of aging, genetic predisposing factors, medicines used for treatment of primary disease (particularly steroids and tumor necrosis factor (TNF) inhibitors), metabolic influences of inflammatory processes, and immobilization due to a primary disease.[17,19,20]

In a study from Türkiye, Hashimoto's thyroiditis was found in 10% of AS patients (n=80), which was higher than healthy controls.[21] Another trial investigated thyroid nodules in biologically-treated AS patients. About 37.5% of TNF inhibitor-treated patients had thyroid nodules; however, none of them revealed a malignant transformation.[22] In a small study, any type of thyroid dysfunction defined according to thyroid stimulating hormone and thyroxine values was found in 27.5% of SpA patients.[23] Hypothyroidism requiring hormone replacement therapy was found to a lesser extent than other autoimmune rheumatic diseases in SpA patients.[24] As seen, data about thyroid dysfunction in SpA is scarce and the definition of thyroid dysfunction is highly variable. Thyroid dysfunction was reported in 5.6% in our study. Definition of thyroid disease was not well defined; therefore, it was not possible to address the type (hypo-or hyperthyroidism, autoimmune thyroid diseases, and partial or total thyroidectomy) of the reported dysfunction. Moreover, the exact numbers may be different if a specifically designed trial is designed for thyroid diseases.

In our study four classical cardiovascular risk factors were analyzed: age, obesity, smoking, and alcohol consumption. The major cardiovascular events (myocardial infarction, stroke, severe peripheral vascular diseases, and heart failure) were infrequent (0.2-3.8%), among which the most frequent was myocardial infarction. None of the categories defined according to these risk factors revealed any significant difference in major cardiovascular events. According to a relatively large study, total percentage of cardiovascular diseases was lower among AS patients using TNF inhibitors users than nonusers (36.2% *vs.* 48.9%).[25] Among these cardiovascular diseases, myocardial infarction was observed in 1.1% of TNF inhibitor users *vs.* 2.9% of nonusers ($p<0.001$); cerebrovascular disease/stroke was observed in 2.3% and 4.0%, respectively ($p<0.001$), and peripheral vascular diseases and venous thromboembolism disorders were observed in 4.0% and 7.5% ($p<0.001$), respectively. This study was performed by analyzing the health care system data, and thus the numbers given reflect more objective than patient-reported numbers of comorbidities as in our study.

Peptic ulcer disease and GI bleeding were reported in 3.8% and 0.6% of subjects in our study, respectively. Peptic ulcer disease is a general term used to describe gastroduodenal ulcers, even for some upper GI discomfort. Consumption of NSAIDs, glucocorticoids, and some other immunosuppressive medication may increase the incidence of GI discomfort, whether or not leading to ulceration. Since this study encompasses patients who are on biologic DMARD treatment, objective relation between the use of the mentioned medications and upper GI complaints could not be established. Inflammatory bowel disease-related SpA was included in our investigation but was not a distinct entity.

Depression, anxiety, and other psychological problems are more frequently encountered among patients with rheumatic diseases.[26-29] In SpA, it is believed that there is a bidirectional mechanism of exacerbation between rheumatologic and psychological symptoms.[26] In a recent European study, diagnoses of depression and anxiety were found in 30% and 33% of patients, respectively.[27] In a trial from Germany, 28% of 1.736 AxSpA patients suffered from moderate to severe depressive symptoms. Higher disease activity, higher level of functional impairment, and poor socioeconomic conditions were related to a depressive state.[28] Indian researchers declared depression symptoms in 36% of AxSpA patients.[29] In a comorbidity analysis of SpA patients, depression was reported as the second most frequent comorbidity (16%) after HT (19%).[15] Moderate to severe depressive symptoms were reported in 15% of SpA patients, while mild symptoms existed in about 40% of SpA patients.[26] As observed, reported prevalence of depression among SpA patients is highly variable and depends on which of the criteria is used for definition. The rate of depression was lower (4.9%) relative to other investigations mentioned above in our trial. This study did not intend to assess depression specifically. Presence of depression was defined according to declaration of patients or a medication used for depression. Patients with mild depressive complaints who did not look for medical care might have been missed in this study, and the real frequency of depression might be underscored. Anxiety was not included as an individual comorbidity.

There were no AIDS and hepatic diseases reported in this trial. The study population was composed of biologically treated SpA patients, and they were regularly screened for infectious, malignant diseases, and any type of systemic functional deterioration before and after the initiation of treatment for safety concerns. The most probable explanation for this situation is the screening process. Additionally, AIDS is considered in the category of a notifiable disease; accordingly, suspected patients undergo a double-check procedure by infectious disease control teams in our country. This may be the other reason why we did not see any AIDS patients in the cohort. Malignant disease was reported in a small percentage of patients (0.6%). None of the malignancy cases was linked to biological treatment. Subsequent follow-up analysis of the BioStar database will enlighten the malignancy risk associated with biological treatments.

Studies on AxSpA revealed that being overweight is related to development of comorbidities, particularly HT.[30] It was also reported that obesity is related to worse outcome measure scores of primary disease and functional status.[30] The development of comorbidities may be related to pathologic processes of the primary rheumatic disease. In addition, traditional risk factors may influence development or accelerate the clinical manifestations of comorbid conditions. Age, sex, and genetic features are nonmodifiable risk factors for comorbidity. But daily lifestyle and individual habits (e.g., smoking, alcohol consumption) are modifiable risk factors. Obesity is considered not only a risk factor for comorbidity development but also a comorbid condition. In our study, the mean age and BMI of females was higher than males. In parallel, mean comorbidity scores were higher among females. Smoking and alcohol consumption were higher among males, but they did not lead to alteration in any of comorbidity measurements. The development of comorbidities is more strongly related to aging and being overweight than smoking and alcohol consumption.

Comorbidities can be collected in two ways: either separately collecting each comorbidity or summarizing the comorbidity information into a single score that provides a parameter. The major advantage of comorbidity indices is reducing all coexisting disorders into a single numerical score, so evaluation of the impact of the comorbidities on the burden of the disease is facilitated. This is the reason why these indices are mainly used in clinical trials or epidemiological studies.[3] Systematic quantification of the comorbidity burden is essential for the clinical management of index diseases.[14] Most of the comorbidity indices were developed for general population; specific indices were developed to be used for specific circumstances. In this study, we have used two different comorbidity indices: CCI and RDCI. The CCI was published in 1987 and based on the mortality rates of 607 patients admitted to the general internal medicine service for a period of one month. The objective was to develop a method for classifying comorbidities that might alter the risk of mortality for use in longitudinal studies.[11] It is accepted as an applicable tool in every situation. In contrast, RDCI was used to quantify the comorbidity burden of patients who have rheumatologic diseases. One of the main differences between CCI and RDCI is the content. The RDCI contains potential comorbidities that are more frequently encountered in the context of rheumatologic diseases.[12] In our study, correlations between these indices was relatively strong ($r=0.731$, $p<0.001$). In the categorical analysis of comorbidity indices in this study, the predefined cut-off value for CCI was 3. There were a relatively small number of patients in the category with CCI ≥3 (n=23). The major components of CCI, which were not detected in our study population, were AIDS, severe hepatic disease, and metastatic solid tumor. As a result, the mean CCI and percentage of patients with a CCI ≥3 were fairly low. The categorization of RDCI by considering the cut-off value of 2 was made semiarbitrarily. The reason for this is the absence of such a definition, except for one study.[14] In our study, the percentage of patients with moderate to severe comorbidity according to RDCI ≥2 was higher (11.03%) than that by the categorization according to CCI ≥3 (1.85%). Although the correlation between these indices is significant, it appears that they are not identical indices. Based on our results, it cannot be decided which one of the used indices is superior. However, it is necessary to define the cut-off values for measured RDCI for a detailed interpretation of the results.

This study was cross-sectional in design. Therefore, the cause-and-effect relationship

between reported comorbidities and primary diseases could not be clarified. Additionally, the relevance of reported comorbid conditions to used biologic drugs could not be clarified by the design of the investigation. Furthermore, the current clinical status of SpA measured by PROMs, disease activity scores, and metrological measurements was not correlated with comorbidity status. One of the most relevant explanations for this situation is the design of the study. Comorbidity status is the cumulative result of aging, chronic disease state, and presence of traditional risk factors, some of which are genetic. The cross-sectional analysis of these conditions may not match each other. The inability to set the cause-and-effect relationship between comorbidities, disease subgroups, and used medication and absence of mortality rates are the main shortcomings. Nevertheless, BioStar is an ongoing project, and we hope that subsequent analyses will delineate these issues. The extraarticular manifestations of SpA and central sensitization syndrome were beyond the scope of this investigation since they were analyzed by other investigators. High number of subjects, detailed definition and recording of comorbidities, quantification of comorbidities by using two different comorbidity indices are the strong aspects of the study.

In conclusion, the most commonly reported comorbidities were HT, DM, thyroid disorders, and depression in Turkish SpA patients by the BioStar database. In general, the frequency of comorbidities and composite comorbidity scores were higher among females, older patients, and overweight patients. The cause-and-effect relationship between comorbidities and SpA could not be clarified since this was a cross-sectional analysis of the database. Since the comorbidity issue is an ample field of medicine, particularly for inflammatory rheumatic diseases, there will always be a need for additional and comprehensive investigations in the field.

Ethics Committee Approval: The study protocol was approved by the Ankara Numune Training and Research Hospital (Date/no: December 13th, 2018/E-182413) and Turkish Medicines and Medical Devices Agency Ethics Committee (Date/no: January 13th, 2019/66175679-514.99-E.6366). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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