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ORIGINAL ARTICLE

Frequency of fibromyalgianess in patients with rheumatoid arthritis and ankylosing spondylitis: A multicenter study of Turkish League Against Rheumatism (TLAR) network

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** The two authors contributed equally to this study.*

ABSTRACT

Objectives: This study aimed to evaluate the frequency of fibromyalgianess, fibromyalgia syndrome (FS), and widespread pain in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and their relationship with clinical and demographic parameters.

Patients and methods: This cross-sectional multicenter trial was performed in 14 centers across Türkiye between June 2018 and November 2019. Out of 685 patients recruited from the accessible population, 661 patients (342 RA, 319 AS; 264 males, 397 females; mean age: 48.1±12.9 years; range, 17 to 88 years) met the selection criteria. In these cohorts, those who did not meet the criteria for FS and had widespread pain (widespread pain index ≥7) were evaluated as a separate group. Clinical status and demographic parameters of patients in both cohorts were evaluated as well as the evaluations of RA and AS patients with widespread pain (widespread pain index ≥7) and RA and AS patients with FS groups. In addition, correlations between polysymptomatic distress scale (PSD) scores and Visual Analog Scale (VAS), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and Disease Activity Score using 28 joint counts for RA patients and VAS, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Ankylosing Spondylitis Disease Activity Score (ASDAS) for AS patients were analyzed.

Results: Frequencies of patients with FS and patients who had PSD scores ≥12 were 34.1% and 44.4% in all RA patients, respectively. Moreover, FS and PSD scores ≥12 were found in 29.2% and 36.9% of all AS patients, respectively. PSD scores of RA patients with FS were higher than all RA patients and RA patients with widespread pain. SDAI and CDAI scores of RA patients with FS were higher than all RA patients and RA patients with widespread pain. Similarly, PSD scores of AS patients with FS were higher than all AS patients and AS patients with widespread pain. ASDAS-erythrocyte sedimentation rate and BASDAI scores of AS patients with FS were found higher than all AS patients and AS patients with widespread pain.

Conclusion: Disease activity scores, including pain in RA and AS, were higher in the presence of FS or fibromyalgianess. It may be related to clinical parameters, but cohort studies with long-term follow-up are needed to reveal causality. Additionally, to avoid overtreatment, coexistence of fibromyalgianess should be kept in mind in patients who have inflammatory diseases such as RA and AS, particularly with intractable widespread pain.

Keywords: Ankylosing spondylitis, fibromyalgia syndrome, fibromyalgianess, polysymptomatic distress scale, rheumatoid arthritis, widespread pain.

Fibromyalgia syndrome (FS) is a chronic widespread pain syndrome characterized by fatigue, sleep disturbances, cognitive, and emotional symptoms. It also coexists with various medical disorders, including irritable bowel syndrome, dysmenorrhea, headache, and temporomandibular disorder. The prevalence ranges between 0.2% and 6% with a female predominance in the general population.[1,2]

Coexistence of FS and various inflammatory rheumatic diseases has been reported in the literature. Rate of this coexistence may be as high as 20% for systemic lupus erythematosus and 50% for primary systemic sclerosis.[3-6] Similarly, there are a number of studies suggesting the coexistence of FS and rheumatoid arthritis (RA), with a prevalence of 20% or greater.[7-12] There are a few studies concerning the prevalence of FS in spondyloarthritis in the literature. The prevalence of FS in patients with ankylosing spondylitis (AS) was reported between 14.9% and 29.6%.[13-15]

More recent studies have shown that same central nervous system processes might contribute to pain in any kind of chronic pain, including osteoarthritis, low back pain, and even inflammatory pain conditions such as RA. This phenomenon is suggested to occur over a continuum rather than being present or absent. It was termed as "fibromyalgianess" by Wolfe,[16] who demonstrated that the degree of FS predicts pain and disability in all rheumatic diseases.[4,17] In this context, over one-third of patients with RA exhibit evidence of fibromyalgianess with higher disability scores and inadequate responsiveness to RA treatment.[18] Both in RA and AS, worse outcome scores might be due to fibromyalgianess or coexisting FS, which in turn cause unnecessary medication or dose elevation. In RA, too many tender points, higher levels of pain, and global severity scores but no increase in joint swelling and laboratory parameters were reported in some studies.[12,19,20] A new scale called polysymptomatic distress scale (PSD), or fibromyalgianess scale, has been proposed to evaluate pain and symptom severity. Widespread pain, which has a separate place in the FS criteria, is defined as pain at least seven out of 19 regions in the body.[12,19,20]

Fibromyalgianess scores and FS prevalence were reported to be high in previous studies regarding rheumatological diseases. The occasional increase in symptoms during treatment, particularly in patients with RA and AS, might be accepted as disease exacerbation or drug unresponsiveness. The current study aimed to investigate the prevalence of fibromyalgianess, FS, and widespread pain, as well as their associations with clinical parameters in patients with RA and AS.

PATIENTS AND METHODS

This cross-sectional, multicenter trial was conducted by the study group of Turkish League Against Rheumatism (TLAR) between June 2018 and November 2019. Fourteen clinics across Türkiye were involved in the trial. Patients who were diagnosed as RA and AS and attended their regular visits were included in the study. All patients with RA fulfilled the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria (2010) for RA, and all patients with AS fulfilled the Assessment of SpondyloArthritis international Society criteria (2009) and the modified New York criteria (1984) for AS. In addition, the 2010 FS diagnostic criteria was used for the diagnosis of FS and fibromyalgianess. The PSD score was calculated by the widespread pain index (WPI) + symptom severity score (SSS). Accordingly, all patients who met the FS criteria had a PSD score ≥12, while patients with a PSD score ≥12 were not always diagnosed with FS. In our study, we evaluated patients with a fibromyalgianess scale score ≥12 as a separate item since Wolfe et al.[19] classified the patients who had higher scores than this cut off value as severe. Widespread pain was defined as patients with a WPI ≥7. Visual Analog Scale (VAS), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and Disease Activity Score using 28 joint counts (DAS28) were calculated for patients with RA, and VAS, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) were calculated for patients with AS.

Rheumatoid arthritis-widespread pain group were defined as RA patients with a WPI greater than 7 but did not meet FS criteria. Additionally,

RA-FS group were defined as RA patients who fully met FS criteria.

The exclusion criteria were as follows: *(i)* being <18 years old, *(ii)* being >65 years old, *(iii)* patients with unstable and complicated diabetes mellitus, hypertension (hypertension and fibromyalgia can be defined as autonomic dysfunction groups, and this may reveal a higher fibromyalgianess score in hypertension patients),[21] hyperthyroidism, and other metabolic diseases at the time of enrollment, and *(iv)* patients who had used or using glucocorticosteroids at the time of enrollment (high fibromyalgianess was associated with persistent glucocorticoid use, independent of inflammatory activity,[18] therefore glucocorticoid use was accepted as an exclusion criterion, as it might affect the results).

Türkiye is a country divided into seven geographical regions (the Aegean [the Western], the Marmara [the Northwestern], the Mediterranean [the Southern], the Black Sea [the Northern], the Central, the Eastern, and the Southeastern regions) and 81 administrative provinces. The selected 14 provinces from seven geographical regions were included as trial centers. The 14 provinces were Adana, Samsun, Istanbul, Antalya, Mersin, Diyarbakır, Bursa, Malatya, Ankara, Trabzon, Izmir, Erzurum, Edirne and Aydın. The number of patients enrolled in the trial was determined in monthly periods to minimize the seasonal effect, as some studies have reported that weather conditions can aggravate fibromyalgia symptoms.[22,23] Thus, five RA and three AS patients were enrolled in each month. In total, 685 patients (349 RA, 336 AS) were recruited from the accessible population, and 661 (342 RA, 319 AS; 264 males, 397 females; mean age: 48.1±12.9 years; range, 17 to 88 years) of these patients met the selection criteria (Figure 1). In both the RA and AS groups, PSD scores were evaluated in patients with widespread pain who did not meet the criteria for FS and who fully met the diagnostic criteria for FS. In addition, correlations between PSD scores and VAS, SDAI, CDAI, and DAS28 were evaluated for RA patients, and VAS, BASDAI, and ASDAS were assessed for AS patients.

Sample size

Initially, it was planned to enroll 623 patients for the project based on a reference study. However, since the number of diagnoses of RA and AS reported from the study centers were not known and considering other possible reasons, including dropouts, the sample size was increased by 10% to 685 patients.

Statistical analysis

All analyses were performed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as

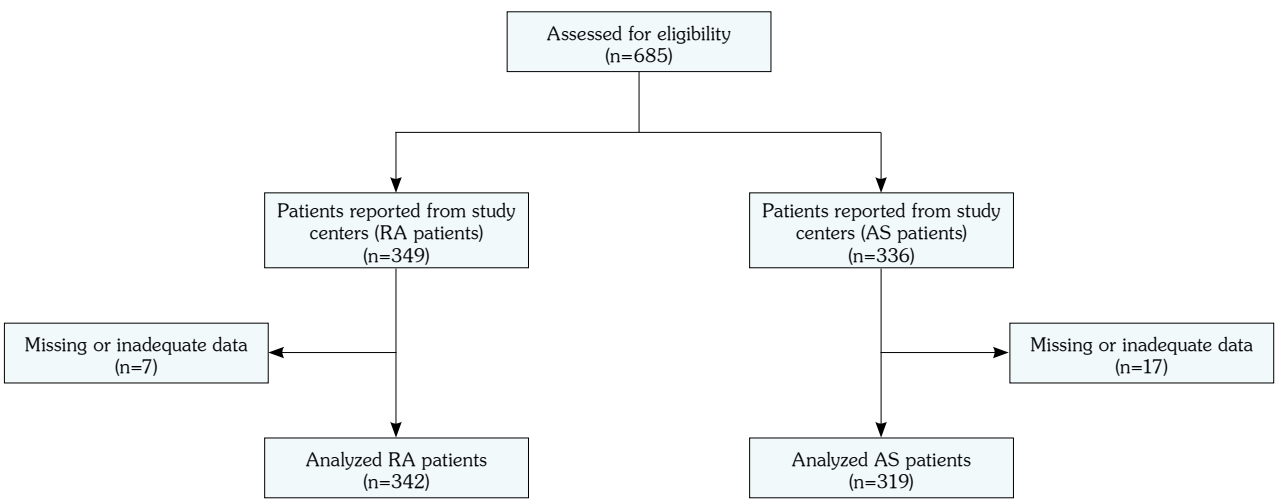

Figure 1. Flowchart of the study.
RA: Rheumatoid arthritis; AS: Ankylosing spondylitis.

Table 1. Clinical variables in patients with RA classified according to pain and fibromyalgia status*

	All RA patients (n=342)			RA-widespread pain patients (n=153 of 342)			RA-FS patients (n=119 of 342)			RA patients without FS and WP (n=187 of 342)		
	%	Mean±SD	Median	%	Mean±SD	Median	%	Mean±SD	Median	%	Mean±SD	Median
Percent of all subjects	100.0			43.8			34.1			55.6		
Age (year)		54.2±11.9			54.4±10.8			54.9±10.9			54.1±12.7	
Sex												
Male	16.9			13.7			10.1			19.6		
Female	83.1			86.3			89.9			80.4		
Disease duration (month)		55.6±67.7			58.0±55.9			61.2±61.0			47.6±84.9	
Pain (range 0-10)		5.1±2.3			6.1±1.9			6.3±2.0			4.2±2.3	
Patient global severity (range 0-10)		5.0±2.2			6.0±1.8			6.2±1.7			4.2±2.1	
WPI (range 0-19)		6.2±4.6			10.6±2.8			10.9±3.0			2.7±2.0	
SSS (range 01-12)		4.8±2.8			6.4±2.6			7.5±1.9			3.5±2.3	
FS research criteria	34.1			76.5			100.0			0.0		
Fibromyalgianess scale	44.4			88.9			100.0			8.8		
Widespread pain	43.8			100.0			98.3			0.0		
Polysymptomatic distress		11.2±6.5			17.0±4.4			18.4±3.9			6.3±3.3	
Polysymptomatic distress			10.0			17.0			18.0			6.0

RA: Rheumatoid arthritis; *FS research criteria; SD: Standard deviation; FS: Fibromyalgia syndrome; WP: Widespread pain; WPI: Widespread pain index; SSS: Symptom severity score; WPI ≥7 and SSS ≥5 or 3 ≤ WPI ≤6 and SSS ≥9; Fibromyalgianess scale: PSD ≥12; Widespread pain: WPI ≥7.

numbers and percentages, whereas continuous variables were summarized as mean and standard deviation. The chi-square test and Fisher exact test were used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. For comparison of continuous variables between two groups, Student's t-test or the Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled. For the comparison of more than two groups, one-way analysis of variance or the Kruskal Wallis test was used depending on whether the statistical hypotheses were fulfilled. For normally distributed data, regarding the homogeneity of variances, Tukey or Games-Howell tests were used for multiple comparisons of groups. For nonnormally distributed data, the Bonferroni-adjusted Mann-Whitney U test was used for multiple comparisons of groups. Pearson correlation coefficient was used to evaluate the correlations between PSD scores and VAS, SDAI, CDAI, and DAS28 for RA patients and VAS, BASDAI, and ASDAS for AS patients. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

In the RA cohort, 153 patients had widespread pain, while 119 fulfilled FS criteria (Table 1). Sex and mean age of all RA patients, RA patients with widespread pain, RA patients with FS, and RA patients without FS and widespread pain are shown in Table 1. The highest scores of PSD were found in RA-FS and RA-widespread pain patient groups (Table 1). Frequencies of patients with FS and patients who had PSD scores ≥12 were also shown in

Table 2. Comparison of demographic data and polysymptomatic distress score in patients with RA

		Polysymptomatic distress score	
	n	Mean±SD	*p*
Sex			0.047
Male	57	9.57±6.01	
Female	285	11.46±6.60	
Smoking			0.035
Never	226	11.67±6.38	
Active smoker	63	11.00±6.58	
Quit smoking	48	9.52±7.01	
Unknown	5	5.20±3.27	
Alcohol consumption			0.804
Never	311	11.18±6.63	
Active consumer	18	11.83±5.88	
Quit consumer	6	9.50±3.61	
Unknown	7	9.57±6.50	
NSAID's			0.002
Non user	274	10.62±6.43	
User	68	13.29±6.56	
Methotrexate			0.814
Non user	94	11.28±6.65	
User	248	11.10±6.50	
Sulfasalazine			0.644
Non user	280	11.07±6.58	
User	62	11.50±6.30	
Biologic agent			0.235
Non user	187	11.53±6.65	
User	155	10.69±6.38	

RA: Rheumatoid arthritis; SD: Standard deviation; NSAID's: Nonsteroidal antiinflammatory drugs.

Table 1. The mean PSD score of RA-widespread pain group was greater than all RA patients group (Table 1). PSD scores of female patients (11.46±6.60) were higher than male patients (9.57±6.01), and there were statistically significant differences between male and female patients (p=0.047, Table 2). In addition, there were statistically significant differences for PSD scores regarding smoking habits (p=0.035, Table 2). PSD scores were higher in RA patients who never smoked compared to RA patients who were active smokers (Table 2). No statistically significant differences were found in PSD scores regarding the alcohol consumption (p=0.804, Table 2). There were statistically significant differences in PSD scores by the means of nonsteroidal anti-inflammatory drug (NSAID) use in patients with RA (p=0.002, Table 2); PSD scores were higher in NSAID users than nonusers (Table 2). There were no statistically significant differences in PSD scores regarding methotrexate, sulfasalazine, and biologic agent users (Table 2). The number of tender and swollen joints were higher in RA patients with widespread pain and FS than RA patients without FS and widespread pain (Table 3). This situation was similar for DAS28, SDAI, and CDAI scores (Table 3). There were weak positive correlations between PSD and DAS28, SDAI, and CDAI scores (r=0.421, r=0.424, and r=0.449, respectively; p<0.001).

In the AS cohort, 121 patients had widespread pain, and 98 patients had FS (Table 4). The mean PSD score of AS patients was 17.7±4.2. The mean PSD score of AS patients without FS and widespread pain are shown in Table 4. Frequencies of patients with FS and patients who had PSD scores ≥12 are shown in Table 4. The mean PSD

Table 3. Correlations of clinical data and polysymptomatic distress in patients with RA

	All RA patients (n=342)		RA-widespread pain patients (n=153 of 342)		RA-FS patients (n=119 of 342)		RA patients without FS and WP (n=187 of 342)			
	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	r*	*p*
Number of tender joints		7.1±6.0		9.0±6.2		9.4±6.4		5.2±5.1	0.358	<0.001
Number of swollen joints		3.9±3.8		4.4±3.9		4.3±3.7		3.3±3.5	0.087	0.250
DAS28 (CRP)		3.7±1.2		4.3±1.1		4.3±1.1		3.2±1.1	0.421	<0.001
Inactive (remission)	21.7		7.8		6.7		33.2			
Low disease activity	15.9		9.8		7.6		21.1			
Moderate disease activity	46.7		57.6		58.8		37.9			
High disease activity	15.7		24.8		26.9		7.9			
SDAI		18.6±11.5		23.7±11.1		24.4±10.9		14.4±10.0	0.424	<0.001
Inactive (remission)	3.5		0.0		0.0		6.3			
Low disease activity	25.0		8.6		6.8		38.4			
Moderate disease activity	48.2		55.9		55.1		42.1			
High disease activity	23.3		35.5		38.1		13.2			
CDAI		17.3±11		22.2±10.6		22.9±10.4		13.3±9.4	0.449	<0.001
Inactive (remission)	3.5		0.0		0.0		6.3			
Low disease activity	20.9		6.6		4.3		32.6			
Moderate disease activity	48.5		52.6		52.5		45.3			
High disease activity	27.1		40.8		43.2		15.8			

RA: Rheumatoid arthritis; SD: Standard deviation; FS: Fibromyalgia syndrome; WP: Widespread pain; DAS; Disease Activity Score; CRP: C-reactive protein; SDAI; Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; * r stands for the correlation coefficient between the measurements and PSD score.

Table 4. Clinical variables in patients with AS classified according to pain and fibromyalgia status*

	All AS patients (n=342)			AS-widespread pain patients (n=153 of 342)			AS-FS patients (n=119 of 342)			AS patients without FS and WP (n=187 of 342)		
	%	Mean±SD	Median	%	Mean±SD	Median	%	Mean±SD	Median	%	Mean±SD	Median
Percent of all subjects	100.0			36.0			29.2			61.9		
Age (year)		41.7±10.7			42.2±9.9			41.1±10.0			41.6±11.1	
Sex												
Male	66.1			57.0			53.1			72.1		
Female	33.9			43.0			46.9			27.9		
Disease duration (month)		70.7±79.5			64.4±64.2			64.4±67.2			84.3±99.1	
Patient global severity (range 0-10)		4.5±2.3			5.8±1.8			5.9±1.9			3.6±2.1	
WPI (range 0-19)		5.5±4.4			10.2±3.2			10.3±3.6			2.7±2.0	
SSS (range 01-12)		4.4±2.8			6.1±2.5			7.4±1.8			3.1±2.1	
FS research criteria	29.2			75.2			100.0			0.0		
Fibromyalgianess scale	36.9			84.3			100.0			7.2		
Widespread pain	36.0			100.0			92.9			0.0		
Polysymptomatic distress		10.1±6.3			16.3±4.9			17.7±4.2			6.1±3.2	
Polysymptomatic distress (median)			9.0			15.0			17.0			6.0

AS: Ankylosing spondylitis; FS: Fibromyalgia syndrome; WP: Widespread pain; SD: Standard deviation; WPI: Widespread pain index; SSS: Symptom severity score; WP: Widespread pain; * FS research criteria: WPI ≥7 and SSS ≥5 or 3 ≤ WPI ≤ 6 and SSS ≥ 9; Fibromyalgianess scale: PSD ≥12; Widespread pain: WPI ≥7.

Table 5. Comparison of demographic data and polysymptomatic distress score in patients with AS

		Polysymptomatic distress score	
	n	Mean±SD	*p*
Sex			0.001
Male	207	9.20±5.88	
Female	112	11.77±6.68	
Smoking			0.447
Never	141	10.39±6.20	
Active smoker	123	9.85±6.24	
Quit smoking	49	9.51±6.47	
Unknown	6	13.50±6.29	
Alcohol consumption			0.289
Never	255	10.31±6.30	
Active consumer	36	10.30±6.72	
Quit consumer	6	9.00±4.64	
Unknown	22	7.68±5.60	
NSAID's			0.012
Non user	151	9.17±5.70	
User	168	10.94±6.68	
Methotrexate			0.263
Non user	309	10.03±6.22	
User	10	12.30±8.17	
Sulfasalazine			0.010
Non user	219	9.46±5.95	
User	100	11.52±6.79	
Biologic agent			0.575
Non user	90	10.42±6.31	
User	229	9.98±6.23	

AS: Ankylosing spondylitis; SD: Standard deviation; NSAID's: Nonsteroidal antiinflammatory drugs.

Table 6. Correlations of clinical data and polysymptomatic distress in patients with AS

	All AS patients (n=319)		AS-widespread pain patients (n=121 of 319)		AS-FS patients (n=98 of 319)		AS patients without FS and WP (n=191 of 319)			
	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	r*	*p*
ASDAS-ESR		2.3±1.0		2.8±0.9		2.9±0.9		1.9±0.8	0.542	<0.001
Inactive disease	13.5		4.1		5.1		19.7			
Moderate disease activity	31.9		14.0		15.3		42.4			
High disease activity	43.3		59.5		55.1		33.3			
Very high disease activity	11.3		22.4		24.5		4.5			
ASDAS-CRP		2.5±0.9		3.1±0.8		3.1±0.8		2.1±0.9	0.568	<0.001
Inactive disease	9.8		1.7		2.0		15.2			
Moderate disease activity	24.6		9.1		6.2		34.3			
High disease activity	50.9		61.2		62.2		44.4			
Very high disease activity	14.7		28.0		29.6		6.1			
Back pain		4.2±2.5		5.8±2.2		6.0±2.2		3.3±2.2	0.599	<0.001
Duration of morning stiffness		2.7±2.8		4.0±2.9		4.2±3.0		1.9±2.3	0.460	<0.001
Peripheral pain/swelling		1.9±2.5		3.2±2.9		3.4±2.9		1.1±1.8	0.540	<0.001
BASDAI (range 0-10)		3.4±2.2		5.1±1.8		5.3±1.8		2.5±1.7	0.711	<0.001
Inactive disease	62.2		28.1		24.5		83.2			
Active disease	37.8		71.9		75.5		16.8			
MASES (range 0-13)		3±3.4		5.4±3.8		5.4±3.8		1.6±2.2	0.596	<0.001

AS: Ankylosing spondylitis; FS: Fibromyalgia syndrome; WP: Widespread pain; SD: Standard deviation; ASDAS; Ankylosing Spondylitis Disease Activity Score; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Index; * r stands for the correlation coefficient between the measurements and PSD score; FS research criteria: WPI ≥7 and SSS ≥5 or 3≤ WPI ≤6 and SSS ≥9; Fibromyalgianess scale: PSD ≥12; Widespread pain: WPI ≥7.

score of AS-widespread pain group was greater than all AS patients group (Table 4). There were statistically significant differences in PSD scores regarding sex, use of NSAIDs, and sulfasalazine (p=0.001, p=0.012, and p=0.010, respectively). Furthermore, PSD scores were higher in nonsmoker patients who did not use biologic agents, but the difference was not statistically significant (Table 5). BASDAI, MASES, ASDAS-erythrocyte sedimentation rate (ESR), and ASDAS-C-reactive protein (CRP) scores and the presence of back pain, peripheral pain, and swelling were higher in AS patients with widespread pain and FS than in AS patients without FS and widespread pain (Table 6). There were moderate positive correlations between PSD and ASDAS-ESR, ASDAS-CRP, back pain, peripheral pain, swelling, and MASES values (r=0.542, r=0.568, r=0.595, r=0.540, and r=0.596, respectively; p<0.001). In addition, a strong positive correlation was found between PSD and BASDAI scores (r=0.711, p<0.001, Table 6).

DISCUSSION

Fibromyalgia syndrome consist of high levels of polysymptomatic distress. Patients with inflammatory rheumatic diseases, including RA and AS, may also have pain in a number of nonarticular sites. These patients may have concomitant FS or mostly have polysymptomatic distress. The current multicenter study attempted to establish the frequency of fibromyalgianess and FS in patients with RA and AS and found a nonnegligible frequency of fibromyalgianess (approximately 40%) in both AS and RA patients. In addition, PSD scores were also correlated with disease activity measures.

According to the 2010 FS diagnostic criteria, it is necessary to have a WPI score ≥7 and SSS ≥5 or a WPI score between 3-6 and SSS ≥9 for the diagnosis of FS.[20] However, in some cases with chronic conditions, specifically with rheumatic diseases, coexisting widespread muscle and soft tissue pain is frequently observed.[3,24] This condition is generally attributed to the exacerbation of the inflammatory disease or coexisting FS. This may be confusing due to the lack of defined objective markers for the diagnosis of FS or laboratory and clinical findings that do not support the disease exacerbation. We suggest that this may be due to the condition of coexisting fibromyalgianess. Although newer diagnostic criteria for fibromyalgia have been developed, the first description of PSD scale, which is one of the main outcome scores in the current study, is based on the 2010 FS diagnostic criteria.

Fibromyalgia syndrome and some rheumatic diseases may coexist. It is suggested that these conditions might share some common inflammatory pathways. One of these theories consists of the neuroimmune pathway, and in one study, the glial marker was found increased in the brain of patients with FS.[25] This finding suggested that there may be a neuroimmune pathology in fibromyalgianess and may occur more prominently in chronic painful conditions such as rheumatic diseases. Additionally, evidence suggested that typical cytokines have effect in the pathogenesis of chronic pain syndromes like FS.[26] For example, interleukin-6, which is one of the major cytokines, could be associated with fatigue, depression, and hyperalgesia by sympathetic system activation, as suggested by Wallace et al.[27] Furthermore, it has been shown that several genes involving the regulation of serotonin and norepinephrine might have an effect in the occurrence of FS, widespread pain, and tenderness.[17]

Ankylosing spondylitis is reported to affect males more than females (approximately 2:1 ratio).[28] However, it has been reported that RA is more common in females than males (3:1 ratio).[29] Similarly, 80 to 90% of patients with FS are female.[30] In the current study, the sex ratio in RA and AS cohorts were found compatible with the literature. While the percentage of males was dominant in all AS patients, this ratio was lower in the group with AS-FS. In addition, while the female sex was higher in all RA patients, this percentage was higher in the RA-FS group. Sex was one of the determinants of coexisting FS and fibromyalgianess in patients with AS or with RA. This condition may be due to various factors. For instance, it was suggested that PSD scores were higher in females who were exposed to any form of abuse at some point in their lives.[31]

Physical and psychological abuse history was not evaluated in this trial. Additionally, FS is one of the important causes of diffuse pain, and the fact that FS is more common in females may explain this situation.

An association between smoking and widespread pain was reported in the literature. This is attributed to the effect of nicotine on the pain pathways or the general damaging effect of tobacco on the musculoskeletal system through vasoconstriction, hypoxia, and defective fibrinolysis.[32] In our study, although there was a significant difference in the subgroup analysis according to smoking habits in RA cohort, the PSD scores between the RA patients who never smoked and RA patients who were active smokers were numerically similar. In addition, no significant difference was found in subgroup analysis according to smoking habits in the AS cohort.

Although there are a number of studies concerning NSAID use in FS, which are mostly related to the treatment of this syndrome, no publications have been found in the literature investigating the relationship between FS and NSAID use. Interestingly, PSD scores were found higher in NSAID users in both AS and RA groups in this study. The majority of patients using NSAIDs might have had intensive pain due to the misconception of inflammatory pain, resulting in the overuse of NSAIDs. However, the high PSD scores in these patients suggested that this may be caused by coexisting FS or fibromyalgianess. In this case, the treatment strategy should be changed.

The duration of pain was longer in RA-FS compared to those with all RA and RA-widespread pain patient groups. This can be explained by the fact that the pain characteristics of FS are more prominent, and the initial symptoms of RA may have been treated as FS for a long time since the initial symptoms were similar to those of FS. In contrast, the duration of disease for AS-widespread pain and AS-FS patients was similar, which was less than in the AS group. This may be related to the high ratio of males in AS and the atypical course of FS.

There were significant correlations between PSD and disease activity scores (DAS28 and BASDAI), but these correlations were not very strong (the highest was r=0.568 in AS and r=0.449 in RA). DAS, SDAI, and CDAI values in patients with RA were evaluated in four subgroups regarding disease activity: inactive disease, low disease activity, medium-moderate disease activity, and high disease activity. It is necessary to discuss DAS since high DAS scores are generally required to progress to further treatment options in patients with RA. In a study of Ranzolin et al.,[33] it is suggested that there is a danger to accepting DAS as "truth" in RA patients who had FS. Wolfe et al.[20] also warned the physicians and insurance companies regarding the misuse of DAS as the sole criterion for initiation and evaluation of anti-tumor necrosis factor therapy in these patients. FS differs from the frequently studied chronic widespread pain concept by its inclusion of fatigue, unrefreshed sleep, cognitive problems, and somatic symptoms. It is reported that FS is a continuum disorder.[2] Therefore, an increase in the PSD score or fibromyalgianess does not always correlate with the increase of disease activity. This condition suggested that although FS contributes to medium-moderate activity scores, RA itself has a primary effect on high disease activity values. This is also true for ASDAS scores in AS.

We found high BASDAI scores in patients with AS-widespread pain and AS-FS groups, as in other studies in the literature.[34-36] This may be explained by the fact that BASDAI is a self-assessed questionnaire, and is independent of the laboratory results. ASDAS-ESR and ASDAS-CRP values were also high in the same groups. In addition, the percentage of patients with high disease activity was greater in the AS cohort. Here, it is important for the clinician to question other symptoms of FS. Otherwise, it may unnecessarily cause a switch to advanced treatment options. The high ASDAS values were also found in some studies,[34] and highly sensitive CRP and calprotectin measurements were recommended for the evaluation of inflammation.[37,38]

The present study had some limitations. First, although fibromyalgianess and FS are reported as different disorders, the distinction between these entities is not clear and not widely accepted. Second, although we included patients with stable metabolic diseases at the time of

enrollment, we did not evaluate the effects of metabolic diseases on FS and fibromyalgianess. The third limitation was the lack of control subjects in the study. Lastly, the study was not prospective in design; thus, we could not report the number of patients with widespread pain or fibromyalgianess that evolved to FS in a definite period.

In conclusion, the prevalence of FS and widespread pain were high in RA and AS patients. This situation might affect the activity scores of these two diseases. In the management of inflammatory rheumatic diseases, particularly in cases where the laboratory values are not proportional to the disease activity or clinical findings, it should be taken into consideration, and the treatment should be planned by considering the concomitant fibromyalgianess and FS to avoid using unnecessary anti-inflammatory and conventional or biologic disease-modifying antirheumatic drugs.

Ethics Committee Approval: The study protocol was approved by the Çukurova University Faculty of Medicine Ethics Committee (date: 02.03.2018, no: 75/43-2018). This study was carried out in accordance with the principles of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cohort studies checklist.

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.

Author Contributions: All authors contributed to the study design, material preparation, data collection, analysis, interpretation and writing of the manuscript and take full responsibility for the integrity of the study and the final manuscript. All authors read and approved the final manuscript.

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