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Original Article

Effects of fibromyalgia on the disease activity and treatment of patients with axial spondyloarthritis

Ruoxi Gao

China Medical University, Liaoning Province, China

Abstract

Objectives: To investigate whether patients with radiologically positive spondyloarthritis (SpA), suffer from comorbid fibromyalgia (FM), and to explore the impact of FM on the clinical manifestations and blood test results of patients with ankylosing spondylitis (AS). **Methods**: 121 patients with spondyloarthritis (SpA) were enrolled in the study. The body function of the patients was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI); the mental health was evaluated using the Hospital Anxiety and Depression Scale (HADS). **Results**: Out of 121 patients with SpA, 111 patients were with axial spondyloarthritis (axSpA) and 11 patients with FM; 10 patients with peripheral SpA and 1 patient with FM. In axSpA, 107 were radiologically positive axSpA patients, 11 were complicated by FM, and 4 were radiologically negative axSpA (nr-axSpA). Among radiologically positive axSpA, the proportion of female patients in the FM group was higher (63.6%, $P<0.05$). The ASDAS-C-reactive protein (CRP), ASDAS-erythrocyte sedimentation rate (ESR), BASDAI, BASFI, and HADS-anxiety score, and HADS-depression score of the FM group were all significantly higher than those of the non-FM group. **Conclusions**: When determining the treatment plan for SpA, the possibility of coexistence of FM should be considered, and adjuvant treatment should be given when necessary.

Keywords: Ankylosing Spondylitis, ASDAS-C-Reactive Protein, Axial Spondyloarthritis, Fibromyalgia, Spondyloarthritis

Introduction

Spondyloarthritis (SpA) is a rheumatic disease with symptoms and signs including inflammatory back pain, enthesitis, dactylitis, and/or peripheral joint involvement. Clinically, SpA is classified into two types: axial SpA (axSpA) and peripheral SpA. The former includes radiographic axSpA (including ankylosing spondylitis (AS)) and non-radiographic axSpA (nr-axSpA). Compared with the modified New York criteria (1984) for ankylosing spondylitis, the Assessment of Spondyloarthritis international Society (ASAS) classification criteria improves the early diagnosis and treatment of axSpA[1,2].

Fibromyalgia (FM) is a disease characterized by chronic generalized musculoskeletal pain, often accompanied by fatigue, non-restorative sleep, cognitive impairment, depression and anxiety. It affects 1%-5% of the population[3,4]. For patients with rheumatoid diseases, the prevalence rate of FM is up to 10-30%[5], and those with comorbid FM suffer from more severe symptoms and signs[6,7]. Moreover, the pain in patients with FM is significant, and the pain even dominates the clinical manifestations, manifested differently in different individuals. Therefore, FM is easy to be missed or misdiagnosed. FM can be comorbid with early rheumatoid arthritis, early spondyloarthritis, polymyalgia rheumatica, myofascial pain syndrome, hyperkinetic syndrome, gastrointestinal diseases, early malignant tumor, and nervous system diseases[8-11], which delays the treatment of FM and affects the prognosis of the disease. The pain of patients can be evaluated based on the latest 2016 American College of Rheumatology (ACR) classification criteria for FM to reduce subjective errors, and the pain can be identified by dividing pain "regions" instead of pain "sites" to reduce miss diagnosis of regional pain syndrome. In addition, the evaluation of systemic pain symptoms can be emphasized,

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Corresponding author: Ruoxi Gao, The First Hospital of China Medical University, No. 155 Nanjing North Street, Heping District, Shenyang 110000, Liaoning Province, China
E-mail: rhhxn9@163.com

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Table 1. The 2016 American College of Rheumatology classification criteria for fibromyalgia (A patient satisfies diagnostic criteria for fibromyalgia if the following 4 conditions are met)[12].

Systemic pain: There is pain in four regions out of the five regions, excluding jaw, chest and abdominal pain.		
Symptoms appear at similar levels for at least 3 months.		
Widespread pain index (WPI) ≥7 and symptom severity (SS) score ≥5 or WPI =4-6 and SS score ≥9.		
The diagnosis of fibromyalgia has nothing to do with other diagnoses, and its diagnosis does not affect other clinical diagnoses.		
1. WPI: The number of regions with pain in the patients last week. The score is between 0 and 19 points.		
Shoulder girdle, left	Hip (hip, greater trochanter), left	Underjaw, left
Shoulder girdle, right	Hip (hip, greater trochanter), right	Chin, right
Upper arm, left	The upper limb of the left leg	Chest
Upper arm, right	The upper limb of the right leg	Abdomen
Left lower arm	Left crus	Upper back
Right lower arm	Crus, right	Lower back, neck
2. Stanford sleepiness scale (SSS)		
(1) Severity of the following three symptoms last week		
Fatigue		
Non-restorative sleep		
Cognitive symptoms		
For the above three symptoms, the following scale indicates the severity last week: 0= no problem; 1= slight or mild problems, usually minor or intermittent; 2= moderate and quite serious problems, frequent and/ or appearing at a moderate level; 3= serious problems, common, persistent and disturbing normal life		
(2) Occurrence of the following three symptoms during the last six months		
Hypogastralgia or colic		
Black mood		
Headache		
Generally speaking, the physical symptoms of patients are scored as follows: 0= no symptoms; 1= mild symptoms; 2= moderate symptoms; 3= severe symptoms.		
The SSS score is the sum of the severity of the three symptoms (fatigue, wakefulness, and cognitive symptoms) plus the severity of the systemic symptoms, and the final score is between 0 and 12 points.		

and the types of somatic symptoms can be simplified. The evaluation methods of somatic symptoms should be defined to avoid influences on the diagnosis of other diseases. However, this method has not been widely used in clinical diagnosis. The 2016 ACR classification criteria for FM are shown in Table 1[12].

FM and AS have the following common characteristics: Family history, chronic pain, fatigue, spinal stiffness, and sleep disorders. Unlike the autoimmune disease AS, FM is usually considered as a mental or psychosomatic disease, a reaction of central sensitization leading to pain allergy. With this disease, the impulses from the afferent fibers depolarize the dorsal horn neurons, and extracellular CA2+ and nitric oxide diffuse into the neurons, causing excessive release of P substance and glutamate, resulting in excessive excitation of neurons and pain from the dorsal horn to the brain. Headache, primary dysmenorrhea, irritable bowel syndrome, restless legs syndrome, and female urethral syndrome are more common in patients with FM than healthy individuals, and uveitis and characteristic lung, heart, kidney and gastrointestinal manifestations can be found in patients with AS. Compared with patients with AS, patients with FM have no obvious abnormality in physical examination except for extensive soft tissue tenderness, and their laboratory and radiological examination results are normal[14,15]. It is not feasible to widely adopt radiology to identify and diagnose FM and AS in clinical practice.

This study was aimed to investigate the incidence of FM in patients with axSpA and analyzed the impact of FM on the disease activity, physiological function, and mental health of patients.

Methods

A total of 121 patients with SpA were enrolled in this study. They were diagnosed with axSpA according to the ASAS classification criteria for axSpA by specialized physicians in the rheumatism outpatient department from September 2019 and May 2020. Among them, there were 111 patients with axial spondyloarthritis (axSpA) and 10 patients with peripheral SpA. In axSpA, there were 107 radiologically positive axSpA patients and 4 radiologically negative axSpA (nr-axSpA) patients. Due to the error caused by too small sample size, this study mainly explored the incidence of

Table 2. Demographic data.

	Mean ± SD	Minimum value	Maximum value
Age (Y)	33.57±11.617	14	64
Body mass index (kg/m2)	23.48±3.374	16.44	36.71
Age of axSpA diagnosis (years)	29.23±11.925	8	63
Course of axSpA (years)	4.45±4.799	0.08	20

Table 3. Comparison of the age of diagnosis, course of disease, and medication regularity.

	Male (Mean ± SD)	Female (Mean ± SD)	P-value
Age of SpA diagnosis	27.26±10.657	31.92±13.537	0.049
Course of SpA (Year)	5.38±5.281	3.43±3.950	0.039
Medication regularity rate (%)	0.95±0.216	0.93±0.252	0.688

Table 4. Inter-group analysis on the age of diagnosis, course of disease, medication regularity based on the comorbidity of FM.

	No FM (Mean ± SD)	Comorbid FM (Mean ± SD)	P-value
Age of AS diagnosis (years)	28.42±11.752	36.24±13.538	0.042
Course of AS	4.62±4.733	4.03±5.961	0.703
Medication regularity rate (%)	0.91±0.302	0.95±0.223	0.60
ESR	15.53±13.790	26.29±27.134	0.032

FM in axSpA and radiologically positive axSpA patients. All participants involved in this study signed informed consent forms, and FM was diagnosed according to the 2016 ACR diagnostic criteria. The examination results of the patients met the requirements of this study, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelets (PLT), and histocompatibility antigen (human leukocyte antigen (HLA) B27). Infection, other rheumatic diseases and malignant tumors were excluded from this study. The disease activity of the patients was evaluated using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASAS-endorsed disease activity score (ASDAS-CRP and ASDAS-ESR), and the function of the patients was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI). Moreover, their mental health was also evaluated using the Hospital Anxiety and Depression Scale (HADS). Patients with AS were assigned into two groups, the FM group, and the non-FM group, and parameters such as age of diagnosis, course of disease, and medication regularity were documented. In the blood test, we recorded the 1-hour ESR, PLT, CRP and immunoglobulins (immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM)) of patients. All patient examinations and evaluations were performed by a clinician under the same conditions to improve the reliability of our data.

Statistical analysis

The measurement data were in normal distribution and expressed by the mean value±standard deviation ($\bar{X}\pm S$). The two-sample paired t test was used for the comparison between groups. $P<0.05$ was considered as statistically significant. SPSS 22 software was used for all statistical analysis.

Results

A total of 121 patients with SpA were enrolled in this study. Based on the 2009 ASAS classification criteria for axSpA, 111 patients were diagnosed with axSpA, including 64 males (57.6%) and 47 females (42.3%) between 14 and 64 years old, with an average age of 33.67±11.617 years, BMI range between 16.44 and 36.71 kg/m^2, and an average BMI of 23.48±3.374 kg/m^2. Their age of diagnosis was between 8 and 63 years old, with an average age of diagnosis of 29.23±11.925 years, and their course of disease was between 0.08-20 years, with an average mean of 4.45±4.799 years (Table 2). There were 4 patients with undifferentiated SpA (3.6%), 15 patients with peripheral joint involvement (13.5%), 6 patients with uveitis (5.4%), and 28 with

Table 5. Comparison of BASDAI score, BASFI score, ASDAS-CRP, ASDAS-ESR, HADS-anxiety, and HADS-depression between two groups.

	The non-FM group (Mean ± SD)	The FM group (Mean ± SD)	P-value
BASDAI	1.46±1.036	5.22±0.671	<0.001
BASFI	0.73±0.672	3.46±0.979	<0.001
ASDAS-CRP	1.69±0.747	3.09±0.719	<0.001
ASDAS-ESR	1.69±0.760	3.25±0.942	<0.001
HADS-anxiety	5.52±3.449	14.18±2.714	<0.001
HADS-depression	6.52±4.097	13.45±2.734	<0.001

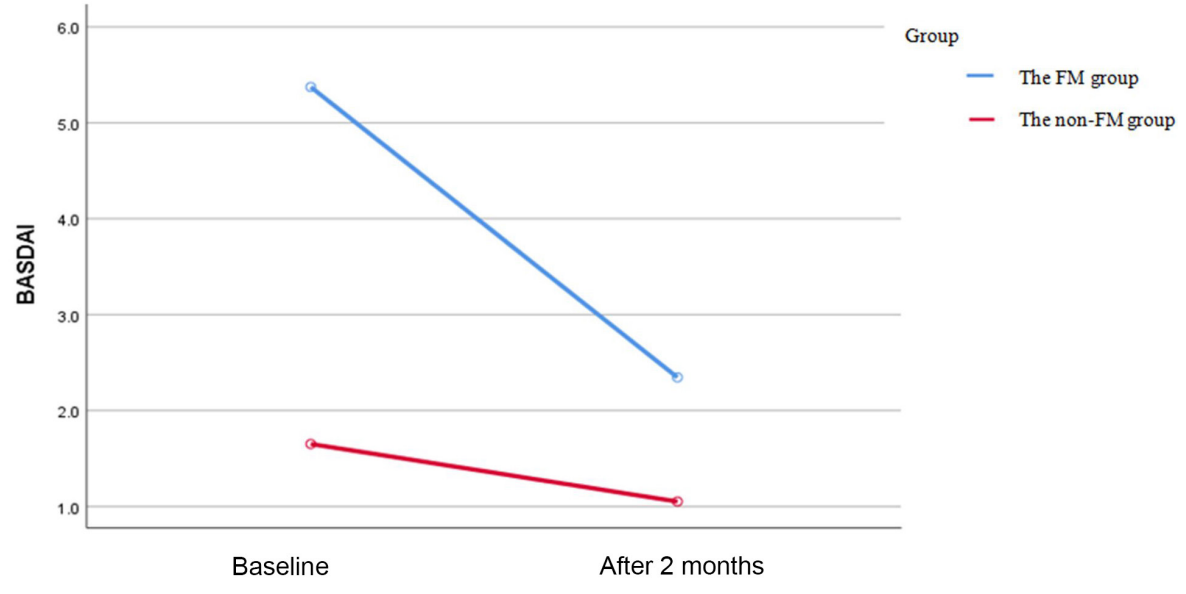

Figure 1. Changes of BASDAI score of patients with AS at two months after treatment.

comorbidity (25.2%). In terms of comorbidity distribution, there were 3 patients with myositis (2.7%), 4 patients with hypertension (3.6%), 2 patients with cardiovascular disease (1.8%), 6 patients with diabetes mellitus (5.4%), 1 patient with hyperthyroidism (0.9%), 5 patients with hypothyroidism (4.5%), 7 patients with renal function impairment (6.3%), and 8 patients with liver function impairment (6.3%). In addition, based on the 2016 ACR diagnosis criteria, 11 of 111 patients with axSpA were diagnosed with FM (9.9%).

Patients were diagnosed with AS according to the New York criteria (1984) for ankylosing spondylitis. In our study, there were significant differences between male and female patients in the age of AS diagnosis and the course of AS. The age of FM diagnosis of female patients was significantly higher than male patients ((31.92±13.537) years vs. (27.26±10.657) years, P=0.049), and the course of AS of female patients was significantly lower compared to male patients ((3.43±3.950) years vs. (5.38±5.281) years, P=0.039).

In addition, there was no significant difference between groups in the distribution of medication regularity rate (P>0.05) (Table 3). It was found that there was no significant difference between the two groups in the course of disease (P>0.05) (Table 4), and the age of disease diagnosis of the FM group was higher than that of the non-FM group ((36.24±13.538) years vs. (28.42±11.752) years, P=0.042). In addition, there was no significant difference between the two groups in the distribution of medication regularity rate (P>0.05). In the blood test, we found that the distribution of these values of the two groups was similar except the 1-hour ESR(all P>0.05). The ESR of the FM group was significantly higher than that of the non-FM group ((26.29±27.134) vs. (15.53±13.790), P=0.032). All patients with AS in our study had HLA B27 test and 101 patients (94.4%) had positive test results. In addition, there was no significant difference between the two groups in the distribution of HLA-B27 positive rate (P>0.05), but there were significant differences in HADS-anxiety, HADS-depression, BASDAI score, BASFI

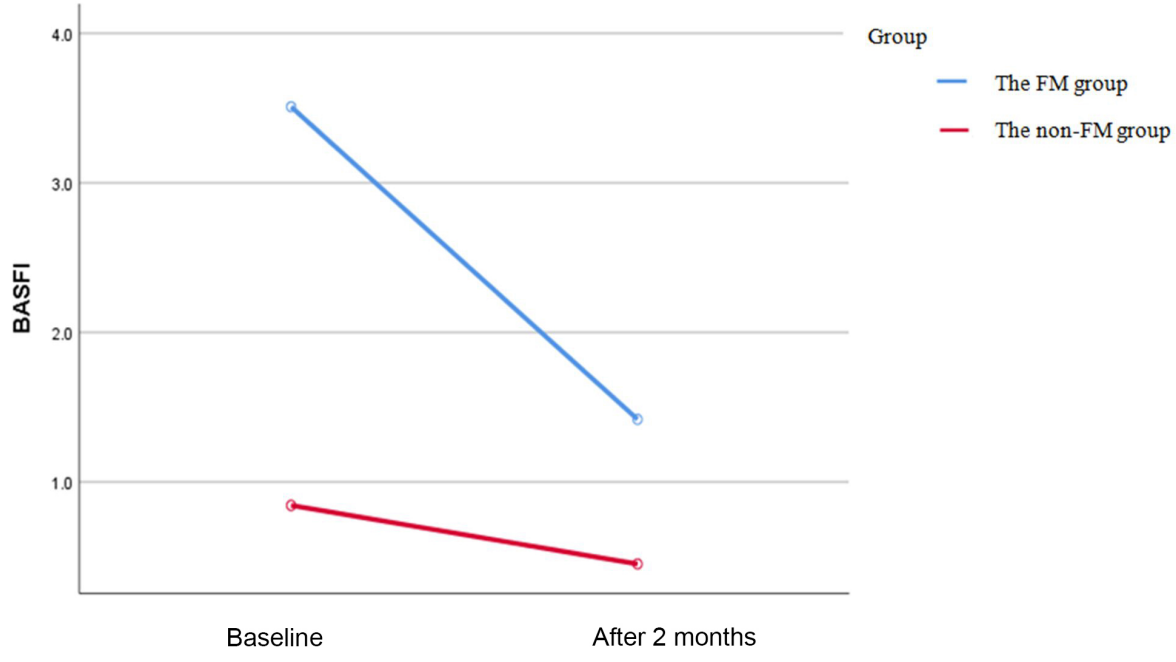

Figure 2. Changes of BASFI score of patients with AS at two months after treatment.

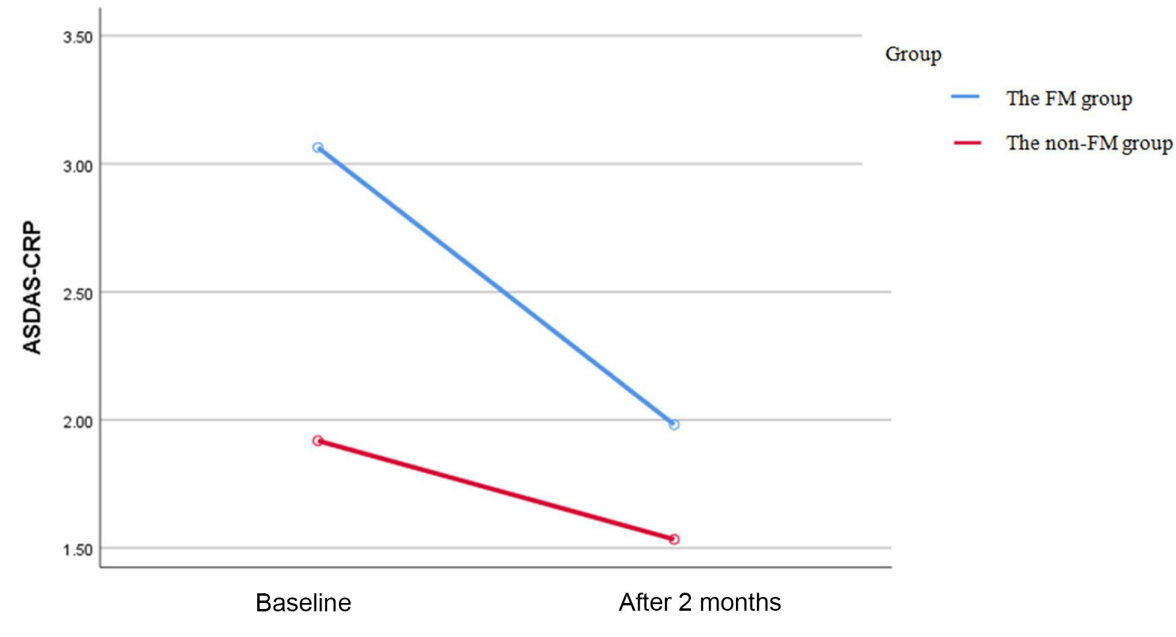

Figure 3. Changes of ASDAS-CRP score of patients with AS at two months after treatment.

score, ASDAS-CRP, and ASDAS-ESR (all $P<0.05$), and these values of patients with comorbid FM were relatively high (Table 5).

Among the 107 radiologically positive SpA, 37 cases withdrew from follow-up due to economic, relocation and other reasons. The 37 patients had no medication side effect. 70 patients with AS were followed up for 2 months, and they were divided into the FM group and the non-FM group. We evaluated the distribution of data of these patients (BASDAI score, BASFI score, ASDAS-CRP, and ASDAS-ESR), finding that the decline of disease-related scores in the FM group and the non-FM group was different, and the decline in the

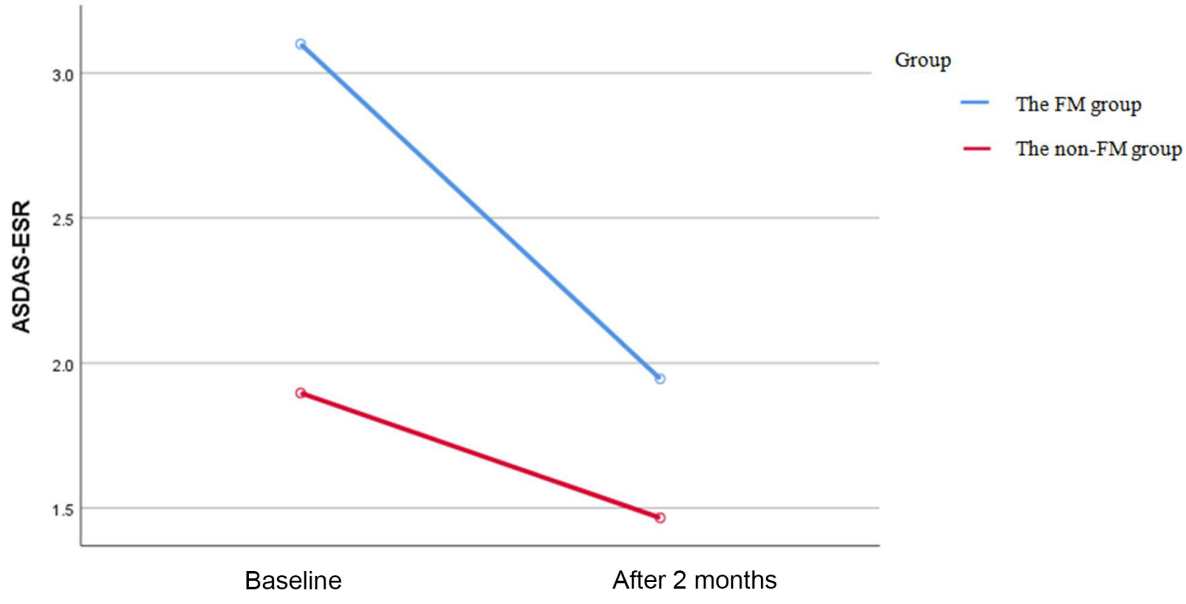

Figure 4. Changes of ASDAS-ESR score of patients with AS at two months after treatment.

FM group was more significant than that in the non-FM group. (Figures 1, 2, 3, and 4). Before the study, we conducted data analysis to determine the minimum number of patients included in our study within the confidence interval of 95%.

Discussion

The aim of this study was to determine whether patients with SpA diagnosed according to the ASAS criteria suffer from comorbid FM, and to evaluate the comorbidity on the clinical symptoms, disease activity, life quality, and inflammatory response of patients.

Clinically, FM is often comorbid with rheumatoid diseases, and its clinical manifestations dominated by pain usually mask the primary diagnostic factors of rheumatoid diseases. Compared with the general population, patients with rheumatoid disease face a significantly higher prevalence rate of FM. In recent years, more and more people have realized the possibility of the coexistence of these two diseases, but only limited studies have emphasized the adverse effects of FM on normal treatment of axSpA.

We enrolled 121 patients with SpA in this study, including 111 patients with axSpA, and found that the incidence of comorbid axSpA and FM was 9.9% (n=11). The incidence of comorbid AS and FM was 10.3% (n=11), which were lower than the incidences reported in some studies. One study by Salaffi et al.[16] diagnosed a total of 402 patients with AS according to the modified New York criteria or with axSpA according to the ASAS criteria and analyzed FM in these patients according to the 2010 ACR criteria for FM. In their study, the incidence of FM in the patients was 14.7%, but the prevalence rate of FM among female patients was as high as 31.3% (P<0.001). In addition, the duration of the disease was similar in patients of different sex: The average course of disease of males was 7.1 years, while that of females was 7.8 years. Moreover, these patients were 51.1±12.2 years old. Another study by Rencber N et al.[17] found 34 patients with comorbid FM out of 125 patients with SpA (29.6%) according to the 2010 ACR criteria for FM diagnosis and the 2009 ASAS criteria for SpA classification. The 34 patients were 41.44±11.65 years old, with age of diagnosis of 35.94±11.46 years old.

The incidence of comorbid axSpA and FM in this study was lower than that in other references. Almost all previous studies used ACR criteria released in 1990, 2011, or earlier for FM diagnosis, but compared with the 2011 diagnosis criteria, the 2016 diagnosis criteria for FM were supplemented with requirements to meet widespread pain standards. Therefore, the study by Wolfe et al.[13] has revealed that the prevalence rate of potential FM in the general German population has decreased from 2.1% to 1.9%. In addition, in our study, the age of enrolled patients was relatively young, and the patients were all yellow race, which may also affect the incidence of FM. Therefore, the results of our study and the above-mentioned studies are not comparable. The specificity of the 2016 criteria was higher, so our study may diagnose patients with FM more accurately, and the incidence of FM in our study was lower. In this case, we believe that our study can be used to guide future use of 2016 ACR criteria for FM diagnosis.

In our study, compared to the age of SpA diagnosis, course of SpA, medication regularity between patients of difference sex, there were significant differences in the age of SpA diagnosis (P=0.049) and course of SpA (P=0.039). The age of diagnosis of AS of female patients was generally higher than that of male patients ((31.92±13.537) years

vs. (27.26±10.657) years), and the course of AS of female patients was slightly shorter than that of male patients ((3.43±3.950) years vs. (5.38±5.281) years). Moreover, there was no significant difference between patients of different sex in medication regularity. Consistent with other references, this study further revealed that the age of SpA diagnosis of female patients was generally higher than that of male patients.

We also evaluated the mental health, physiological function, and disease activity of the patients, and tried to understand how FM changes these parameters. A review of the disease activity (BASDAI, ASDAS-CRP, and ASDAS-ESR) and function (BASFI) score revealed that there were significant differences between the FM group and the non-FM group in the four aspects (all P<0.001). The scores of the FM group were all higher than those of the non-FM group, indicating the deterioration of the disease. Similar to our study, Haliloglu et al.[18] have found that FM affects the BASDAI and BASFI scores of patients with AS, and the scores of patients with comorbid AS and FM are higher. Mental health problem is one of the reasons for the decline in patients' life quality, which depends on various factors. FM accompanying AxSpA leads to a further decline in mental health. Our study showed that HADS-anxiety and HADS-depression scores of the FM group were significantly higher than those of the non-FM group (P<0.05). Similarly, one study by Redeker et al.[19] has shown that patients with axSpA face a significantly higher incidence of depressive symptoms than healthy controls.

To sum up, as mentioned in references, patients with AS tend to suffer from FM, and FM has a negative impact on the patients' functional status, disease activity, and mental health level. However, the incidence of FM in patients with AS in our study was lower (9.9%). In short, when diagnosing patients with SpA, consideration should be given to the possibility of comorbid FM, and FiRST Scale and 2016 ACR criteria for FM diagnosis should be adopted reasonably to improve the accuracy of FM diagnosis. Early diagnosis and treatment are conducive to improving the prognosis of the disease and reducing the occurrence of complications. When FM is concurrent, necessary treatment should be supplemented to improve the treatment curative effect on SpA.

Ethics approval

The study was approved by the Ethics Committee of The First Hospital of China Medical University.

Consent to participate

Written informed consent were obtained from all the patients and/or guardians.

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