Fatigue in Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Analysis from a Longitudinal Observation Cohort

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ABSTRACT. ***Objective.*** In this study, we aimed to address the prevalence of fatigue, its associated factors, and the effect of tumor necrosis factor inhibitors (TNFi) on this subgroup of patients in a large axial spondyloarthritis (axSpA) cohort.

Methods. The study included 681 patients [ankylosing spondylitis (AS) and nonradiographic axSpA (nr-axSpA)]. The Fatigue Severity Scale (FSS) and the Bath AS Disease Activity Index question 1 (BASDAI Q1) indices were used for fatigue assessment. Severe fatigue was defined as an FSS ≥ 4 or a BASDAI Q1 ≥ 5. Disease activity, function, and quality of life (QoL) measures were recorded. Patients who had been treated with TNFi were identified, and baseline and followup data were analyzed.

Results. Of the cohort, 67.3% had severe fatigue, and the prevalence was similar between AS (67.2%) and nr-axSpA (68.2%). Severely fatigued patients tended to have higher disease activity scores, increased acute-phase proteins, and decreased QoL measures. TNFi therapy was associated with improvement in disease activity, and although this treatment led to significantly decreased fatigue scores, this reduction was not optimal in the majority of patients with 80% continuing to have severe fatigue according to their posttreatment scores. Health Assessment Questionnaire, mean scores of BASDAI Q5 and Q6, and BASDAI enthesitis were independent predictors of fatigue severity.

Conclusion. Fatigue is a common symptom in axSpA, and the burden of fatigue among patients with nr-axSpA is similar to that seen in AS. While biologics are effective in improving disease activity, their effect on fatigue is more limited. In axSpA, fatigue remains unresponsive to TNFi in nearly 80% of patients. (First Release November 1 2015; J Rheumatol 2015;42:2354–60; doi:10.3899/jrheum.150463)

Keyword Indexing Terms:
ANKYLOSING SPONDYLITIS QUALITY OF LIFE INFLAMMATION
FATIGUE TUMOR NECROSIS FACTOR-α SPONDYLOARTHROPATHIES

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton. Fatigue, one of the major clinical features of rheumatic diseases, is defined as a state of reduced muscle capacity and decreased work ability accompanied by feelings of tiredness, weariness, and lack of energy[1,2]. In addition to pain and stiffness, fatigue is a major clinical feature of AS, yet it has often been ignored in clinical practice[1,2,3]. On the other hand, fatigue forms one of the components of the Bath AS Disease Activity Index (BASDAI), which is commonly used for defining disease activity in AS[4]. Thus, increased fatigue levels may yield higher BASDAI scores and may affect decision making regarding treatment. AS can adversely affect quality of life (QoL), as well as the psychological and economic status of patients[5]. Fatigue is a common problem even in the population at large, with 14–25% of healthy subjects complaining of fatigue[6]. Fatigue is reported in more than half of patients with AS[1,2,3,7,8,9,10,11,12]. Current understanding of fatigue and its related factors in axial spondyloarthropathy (axSpA) is still limited. Although fatigue is a key element of disease activity scores in AS, the effect of pharmacological therapy is incompletely understood. Better understanding of factors that exacerbate or ameliorate fatigue can provide valuable clues for the optimal management of axSpA. In our

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study, we aimed to address the prevalence of fatigue, its associated factors, and the effect of TNFi on this subgroup of patients in a large axSpA cohort.

MATERIALS AND METHODS

Patients. The patients were drawn from the database of the spondylitis clinic. This database was derived from a longitudinal observation cohort composed of all consecutive patients seen between 2003 and 2014. The referral sources for the spondylitis clinic included community rheumatologists, family physicians, gastroenterologists, and ophthalmologists. Patients with axSpA were evaluated according to a standard protocol in which full demographic, clinical, and laboratory details were recorded at yearly intervals. For our current study, we included subjects who were ≥ 18 years old and had been diagnosed with AS[13] or nonradiographic axSpA (nr-axSpA)[14]. Our study was approved by the hospital's Research Ethics Board.

Outcome assessments. The primary outcome measure in our study was the Fatigue Severity Scale (FSS), which measures motivation, physical activity, and social and functional effects of fatigue. FSS consists of 9 questions, scored on a 0–10 numerical rating scale, and the final value is the mean of all items[15]. Fatigue score was also recorded from the BASDAI question 1 (BASDAI Q1)[4]. Disease activity was evaluated by the BASDAI[4] and the AS Disease Activity Score (ASDAS)[16] indices. Functional activity was determined by the Bath AS Functional Index (BASFI) score[17]. Radiological changes were evaluated by using modified Stokes AS Spinal Score (mSASSS)[18]. QoL and health status were assessed by the AS Quality of Life (ASQoL)[19] and the EQ-5D[20] health questionnaires. The Medical Outcomes Study Short Form-36 (SF-36)[21] and the Health Assessment Questionnaire (HAQ)[22] were used to assess the functional health and well-being status of the patients. Besides clinical and laboratory features, we also identified patients who had been treated with TNFi. Prior to starting a biologic, as part of protocol, all patients received baseline blood work and were reviewed after 3 months of therapy to evaluate the response to treatment. Responses at 3 months were analyzed for our study.

Definition of variables. Severe fatigue was defined as a value of ≥ 4 based on the FSS[15] or ≥ 5 according to the BASDAI Q1[12,23]. Total severe fatigue is defined as patients who have total FSS ≥ 4 or BASDAI fatigue ≥ 5. BASDAI inflammation refers to the mean of BASDAI questions 5 and 6. BASDAI spinal pain, arthralgia, and enthesitis refer to questions 2, 3, and 4, respectively. Anemia was defined as a hemoglobin level < 130 g/l in men and < 120 g/l in women. BASDAI ≥ 4 was used to define high disease activity.

Statistical analysis. A Kolmogorov-Smirnov test was used to test for normality. The main outcome variables of the FSS and BASDAI Q1 showed non-normal distribution. Data were expressed as median and interquartile range (IQR) for continuous variables or as percentages of the total for categorical variables. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 22. The Mann-Whitney U test was used for comparisons between 2 groups of continuous variables. The chi-squared test was performed to compare categorical variables. The relationships between different variables were analyzed by the Spearman correlation test.

According to Dancey and Reidy categorization, a correlation coefficient of 0.1–0.3 represents a weak correlation, 0.4–0.6 represents a moderate correlation, and 0.7 or larger represents a strong correlation[24]. Binary logistic regression analysis (method = ENTER) was used to identify the factors independently associated with total severe fatigue score. The dependent variable, total severe fatigue score, which had binary response, was coded 0, 1. Variables that included a fatigue domain in the respective questionnaires (total BASDAI, SF-36, and ASQoL) were excluded to avoid circularity. Preliminary analysis of the data was performed to check the assumptions of logistic regression regarding the selected predictors of our study. ASDAS-C-reactive protein (CRP), BASDAI inflammation, BASDAI spinal pain, BASDAI arthralgia, BASDAI enthesitis, BASFI, HAQ, CRP, sex, and anemia were subjected to linear regression analysis to evaluate multicollinearity among the predictors or the independent variables. The results of the analysis showed that ASDAS-CRP, spinal pain, and BASFI had a tolerance statistic below 0.2. Thus, as a violation of multicollinearity assumption, these variables were excluded from the model[25]. Baseline and followup comparison of the patients were done by using the Wilcoxon signed-rank and McNemar tests. A double-tailed p value of < 0.05 was considered statistically significant.

RESULTS

Demographics and disease characteristics. There were 681 patients (489 men and 192 women) in our study. The median age of the patients was 40.5 (IQR 31–51) years. Sixty-six out of 681 patients (9.7%) were diagnosed with nr-axSpA. The median disease duration of the group was 8 years (IQR 3–16) and 77.7% were HLA-B27–positive. Nearly half the patients (48.2%) were receiving TNFi therapies. The median FSS was 4.7 (IQR 2.6–7.4) and the median fatigue level according to BASDAI Q1 was 5 (IQR 2–7). According to the FSS ≥ 4 and BASDAI Q1 ≥ 5, 58.4% and 54.9% of the group were classified as severely fatigued, respectively. The frequency of total severe fatigue (patients who have total FSS ≥ 4 or BASDAI fatigue ≥ 5) was 67.3. Table 1 summarizes the clinical and laboratory characteristics of the patients.

Comparison of severe versus low fatigue patients. Comparison of patients with severe (n = 458) versus low (n = 223) fatigue states revealed that these factors were significantly higher in the severely fatigued subset: enthesitis, arthritis, acute-phase measures (CRP and ESR), ASDAS-CRP, total BASDAI, BASDAI inflammation, BASDAI spinal pain, BASDAI arthralgia, BASDAI enthesitis, BASFI, HAQ, ASQoL, and age ($p < 0.05$). SF-36 mental component summary (MCS), SF-36 physical component summary (PCS), and EQ-5D indices were significantly higher in the low fatigue group ($p < 0.05$; Table 1). Between the groups, there were no differences in sex, disease duration, anemia, uveitis, inflammatory bowel disease, mSASSS, or TNFi use ($p > 0.05$).

Comparison of patients with AS and nr-axSpA. Comparison of patients with AS (n = 615) and nr-axSpA (n = 66) revealed that fatigue scores obtained from both the FSS and BASDAI Q1 revealed similar degrees of fatigue between the groups ($p > 0.05$; Table 2). The number of patients with severe fatigue calculated from the FSS or the BASDAI Q1 or the combination of both these variables showed similar frequencies between the disease subtypes ($p > 0.05$). In addition, there were no differences between AS and nr-axSpA with respect to disease activity (BASDAI, BASDAI inflammation, ASDAS-CRP), function (BASFI), spinal pain (BASDAI Q2), arthralgia (BASDAI Q3), enthesitis (BASDAI Q4), QoL indices (HAQ, ASQoL, EQ-5D, SF-36 MCS, and SF-36 PCS), and drug usage (NSAID or TNFi; $p < 0.05$). Table 2 summarizes the characteristics of the patients with AS and nr-axSpA.

Correlation analysis. On correlation analysis, patients with severe fatigue (BASDAI Q1 ≥ 5 or FSS ≥ 4) showed signifi-

Table 1. Comparison of patients with severe and low fatigue scores. BASDAI inflammation refers to the mean of BASDAI questions 5 and 6. BASDAI spinal pain, arthralgia, and enthesitis refer to the questions 2, 3, and 4, respectively. Severe fatigue is defined for patients who have total FSS ≥ 4 or BASDAI fatigue ≥ 5. For continuous variables, data are expressed as median (interquartile range). Other data are % unless otherwise specified.

Variables	Total, n = 681	Severe FSS, n = 458	Low FSS, n = 223	p
Age, yrs	40.5 (31–51)	42 (32–52)	38 (29–49)	0.04
Male/female	71.9/28.1	69.7/30.3	76.6/23.4	0.08
Diagnosis, AS/nr-axSpA	90.3/9.7	90.2/9.8	90.6/9.4	1
Disease duration, yrs	8 (3–16)	8 (3–17)	8 (4–16)	0.28
Enthesitis	6.6	8.1	3.6	0.003
Arthritis	43.5	50.1	29.8	< 0.0001
IBD	11.1	12.7	7.8	0.07
Uveitis	25.1	25.2	24.9	1
Anemia	18.5	19.4	16.7	0.48
CRP, mg/l	3 (3–10)	3 (3–12)	3 (3–7)	0.001
ESR, mm/h	6 (3–15)	7 (3–18)	5 (2–11)	< 0.0001
HLA-B27	77.7	77.1	78.9	0.61
Total BASDAI	4.1 (2–6.3)	5.6 (3.8–6.9)	1.6 (0.8–2.6)	< 0.0001
ASDAS-CRP	2.5 (1.7–3.5)	3 (2.3–3.8)	1.6 (1.2–2.1)	< 0.0001
BASDAI inflammation	4 (1.5–6.5)	5 (3–7.5)	1.5 (0.5–3)	< 0.0001
BASDAI spinal pain	5 (2–7)	7 (4–8)	2 (1–4)	< 0.0001
BASDAI arthralgia	3 (1–6)	4 (2–7)	1 (0–2)	< 0.0001
BASDAI enthesitis	3 (1–7)	5 (2.8–7)	1 (0–2)	< 0.0001
BASFI	2.8 (0.9–5.4)	4.2 (2–6.6)	0.8 (0.1–2)	< 0.0001
mSASSS	6.5 (0–31.2)	6 (0–33.3)	8 (0.8–22.5)	0.96
Biologic use	48.2	48.8	47	0.68
NSAID use	69.9	72.9	63.8	0.02
HAQ	0.5 (0.1–1)	0.75 (0.4–1.1)	0 (0–0.4)	< 0.0001
ASQoL	6 (1–12)	10 (5–14)	1 (0–3)	< 0.0001
EQ-5D	0.8 (0.6–0.8)	0.7 (0.4–0.8)	0.8 (0.8–1)	< 0.0001
SF-36 MCS	48.8 (37.1–56.3)	43.2 (33.3–52.4)	56.3 (51.1–59)	< 0.0001
SF-36 PCS	38.6 (30.5–48.9)	33.5 (27.6–41.5)	49.3 (41.1–54.1)	< 0.0001

AS: ankylosing spondylitis; BASDAI: Bath AS Disease Activity Index; FSS: Fatigue Severity Scale; nr-axSpA: nonradiographic axial spondyloarthritis; IBD: inflammatory bowel disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ASDAS: AS Disease Activity Score; BASFI: Bath AS Functional Index; mSASSS: modified Stokes AS Spinal Score; NSAID: nonsteroidal antiinflammatory drugs; HAQ: Health Assessment Questionnaire; ASQoL: AS quality of life; SF-36: Medical Outcomes Study Short Form-36; MCS: mental component summary; PCS: physical component summary.

cant ($p < 0.05$), moderate, and positive correlations with total BASDAI, BASDAI inflammation, BASDAI spinal pain, BASDAI arthralgia, BASDAI enthesitis, ASDAS-CRP, BASFI, ASQoL, and HAQ (r 0.65, 0.5, 0.56, 0.46, 0.5, 0.57, 0.55, 0.64, and 0.52, respectively), and moderate negative correlations with SF-36 PCS, SF-36 MCS, and EQ-5D (r –0.54, –0.49, and –0.56). There were significant ($p < 0.05$) but weak relations with enthesitis, arthritis, ESR, and CRP (r 0.08, 0.19, 0.16, and 0.14, respectively). When correlations were analyzed between both fatigue evaluation indices (FSS and BASDAI Q1), it was observed that both scales demonstrated strong correlations with each other ($p < 0.0001$, r 0.77).

Regression analysis. Logistic regression was conducted to assess whether the 7 predictor variables — BASDAI inflammation, BASDAI arthralgia, BASDAI enthesitis, HAQ, anemia, sex, and CRP — significantly predicted total severe fatigue. When all variables were considered together, they significantly predicted the dependent variable: chi-square = 211.83, df = 7, n = 525, $p < 0.0001$. The strongest predictor was HAQ. The OR for HAQ was 5.6, i.e., the odds of severe fatigue is increased by 5.6 for each unit increase in total HAQ score. Other predictors that made significant contribution to the model were the BASDAI inflammation and BASDAI enthesitis domains with a recorded OR of 1.3 and 1.2, respectively. Table 3 represents the summary of regression analysis.

Effect of TNFi therapy on fatigue. Comparison of baseline (n = 139) and followup (n = 134) data revealed that baseline FSS and BASDAI fatigue values significantly decreased after TNFi treatment (6.3, IQR 1.1–8.4 vs 5.8, IQR 2.8–8.2, p = 0.04 and 7, IQR 5–8 vs 5, IQR 2–7, $p < 0.0001$, respectively). The numbers of total patients with severe fatigue were also significantly reduced after the treatment (87.8% vs 72.7%, $p < 0.0001$). In accordance with the decreasing fatigue scores,

Table 2. Comparison of patients with AS and nr-axSpA. BASDAI inflammation refers to the mean of BASDAI questions 5 and 6. BASDAI fatigue, spinal pain, arthralgia, and enthesitis refer to the questions 1, 2, 3, and 4, respectively. Total severe fatigue is defined for patients who have total FSS ≥ 4 or BASDAI fatigue ≥ 5. For continuous variables, data are expressed as median (interquartile range). Other data are % unless otherwise specified.

Variables	AS, n = 615	nr-axSpA, n = 66	p
Age, yrs	41 (31–52)	39 (27.5–48.5)	0.07
Male	74.5	47.5	< 0.0001
Disease duration, yrs	8 (4–17)	4 (2–8)	< 0.0001
Enthesitis	6.5	7.6	0.79
Arthritis	43	47.6	0.51
IBD	11.3	9.5	0.83
Uveitis	25.5	21.5	0.55
HLA-B27	78.5	70	0.14
FSS	4.7 (2.6–7.4)	4.7 (2.6–7.5)	0.77
Severe fatigue according to FSS	58.9	54.5	0.51
BASDAI fatigue	5 (2–7)	5.5 (2–8)	0.54
Severe fatigue according to BASDAI fatigue	54.1	62.1	0.24
Total severe fatigue	67.2	68.2	1
CRP, mg/l	3 (3–11)	3 (3–3)	< 0.0001
ESR, mm/h	7 (3–15)	5 (3–10)	0.06
BASDAI	4.1 (2–6.4)	4.3 (2.4–6.3)	0.68
ASDAS-CRP	2.5 (1.7–3.5)	2.5 (1.9–3.1)	0.43
BASDAI inflammation	4 (1.5–6.5)	4.5 (1.5–7.1)	0.42
BASDAI spinal pain	5 (2–7)	6 (3–7)	0.32
BASDAI arthralgia	3 (1–6)	3 (1–6)	0.73
BASDAI enthesitis	3 (1–7)	3 (0–6.3)	0.42
BASFI	2.8 (1–5.6)	2.7 (0.7–4.6)	0.32
Biologic use	48.7	43.5	0.51
NSAID use	69.6	73	0.67
HAQ	0.5 (0.1–1)	0.5 (0.1–0.9)	0.79
ASQoL	6 (1–12)	6 (2–12.5)	0.79
EQ-5D	0.8 (0.6–0.8)	0.8 (0.5–0.8)	0.42
SF-36 MCS	49 (37.2–56.3)	48 (36–56)	0.64
SF-36 PCS	38.7 (30.7–48.9)	37 (29.6–48.7)	0.55

AS: ankylosing spondylitis; nr-axSpA: nonradiographic axial spondyloarthritis; BASDAI: Bath AS Disease Activity Index; FSS: Fatigue Severity Scale; IBD: inflammatory bowel disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ASDAS: AS Disease Activity Score; BASFI: Bath AS Functional Index; NSAID: nonsteroidal antiinflammatory drugs; HAQ: Health Assessment Questionnaire; ASQoL: AS quality of life; SF-36: Medical Outcomes Study Short Form-36; MCS: mental component summary; PCS: physical component summary.

BASDAI total and BASDAI inflammation variables were significantly reduced after TNFi use (6.6, IQR 4.8–7.4 vs 3.5, IQR 1.9–6.2, p < 0.0001 and 7, IQR 5–8.5 vs 3, IQR 1.5–6, p < 0.0001, respectively). TNFi treatment resulted in a significant decrease in the percentage of patients with high disease activity (82% vs 46.8%). Table 4 demonstrates the comparison of patients before and after TNFi treatment.

DISCUSSION

In our current study, we demonstrated that 67.3% of patients with axSpA had severe fatigue, and that patients with AS and nr-axSpA were equally affected. We also found that severely fatigued patients tended to have higher disease activity and functional indices and impaired QoL measures. TNFi therapy was associated with improvement in disease activity, and although this treatment led to significantly decreased fatigue scores, this reduction was not sufficient in the majority of patients, with 80% continuing to have severe fatigue according to their posttreatment scores.

Fatigue continues to be a frequent and sometimes disabling aspect of axSpA. It has a major effect on many aspects of QoL and sense of well-being. Previous studies suggest that up to 70% of patients with AS are fatigued[1,3,10]. There are a number of tools for assessing fatigue in AS. Among them, the most frequently used is the first item of the BASDAI. Some studies have also used more comprehensive scales such as the FSS and the multidimensional assessment of fatigue scale[1,12,23]. In our current study, we evaluated fatigue by using the FSS and BASDAI Q1. According to these indices, we identified 58.4% and 54.9% of our patients as having severe fatigue, respectively. When we evaluated all patients who had BASDAI Q1 ≥ 5 or FSS ≥ 4, we showed that severe fatigue was present in the 67.3% of the patients with axSpA. There was a strong correlation between FSS and BASDAI Q1, suggesting that these indicators are measuring the same events. Both indices revealed nearly similar frequencies of fatigue in patients with axSpA. According to these findings, the more time-consuming and comprehensive FSS may be replaced by the BASDAI Q1 for future studies of fatigue in axSpA.

Fatigue is a complex entity resulting from various factors. The high frequency of fatigue in inflammatory rheumatic diseases suggests that fatigue may be a result of inflammation-driven mechanisms. In our study, we found that fatigue levels as defined by subjective fatigue scores were positively correlated with acute-phase proteins (ESR, CRP), BASDAI, mean scores of BASDAI Q5 and Q6, and ASDAS-CRP. These variables were also significantly higher in the severe fatigue subset. In our regression model we did not include total BASDAI because this is a composite index that also contains a fatigue domain. We also excluded ASDAS-CRP because there was a collinearity with severe fatigue. According to our results, mean score of BASDAI Q5 and Q6 independently predicted the severe fatigue, but we did not find such a relation with CRP. The results also suggested that disease activity, obtained from self-reported measures, may be partly involved in severe fatigue. Our results are consistent with the previous published studies on this subject[7,11,12,26,27].

Previous studies reported an association between sex, enthesitis, and arthritis with fatigue. These studies have shown that severe fatigue is more common in women than men[1,8]. Our data are also in agreement with the current literature showing a predominance of fatigue among female patients.

Table 3. Logistic regression predicting the likelihood of total severe fatigue. Total severe fatigue is defined for patients who have total FSS ≥ 4 or BASDAI fatigue ≥ 5. BASDAI inflammation refers to the mean of BASDAI questions 5 and 6. BASDAI enthesitis refers to the question 4.

Variables	β	Standard Error	OR	95% CI	p
HAQ	1.7	0.37	5.6	2.7–11.5	< 0.0001
BASDAI inflammation	0.24	0.06	1.3	1.1–1.4	< 0.0001
BASDAI enthesitis	0.15	0.06	1.2	1.03–1.3	0.01
BASDAI arthralgia	0.12	0.06	1.1	0.99–1.3	0.06
Anemia	–0.5	0.34	0.61	0.31–1.2	0.14
Females	0	0.27	1	0.59–1.7	0.99
CRP	–0.01	0.015	0.98	0.96–1.01	0.47

FSS: Fatigue Severity Scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

Table 4. Effect of TNFi therapy on fatigue scores. Wilcoxon signed-rank and McNemar tests are used for the comparison of pre- and after treatment values. BASDAI inflammation refers to the mean of BASDAI questions 5 and 6. Total patients with severe fatigue is defined as patients who have total FSS ≥ 4 or BASDAI fatigue ≥ 5. For continuous variables, data are expressed as median (interquartile range). Other data are % unless otherwise specified.

Variables	Baseline, n = 139	After TNFi, n = 134	p
BASDAI total	6.6 (4.8–7.4)	3.5 (1.9–6.2)	< 0.0001
BASDAI inflammation	7 (5–8.5)	3 (1.5–6)	< 0.0001
Patients with BASDAI ≥ 4	82	46.8	< 0.0001
FSS	6.3 (1.1–8.4)	5.8 (2.8–8.2)	0.04
Severe fatigue according to FSS	78.4	69.3	0.04
BASDAI fatigue	7 (5–8)	5 (2–7)	< 0.0001
Severe fatigue according to BASDAI fatigue	77.7	51.8	< 0.0001
Total patients with severe fatigue	87.8	72.7	< 0.0001

TNFi: tumor necrosis factor inhibitors; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; FSS: Fatigue Severity Scale.

Several reports have suggested a relationship between enthesitis, arthritis, and fatigue in AS[11,28]. In our current study, we also showed that both clinically documented and self-reported peripheral arthritis and enthesitis were more prevalent among the patients with severe fatigue. We also showed self-reported enthesitis, as assessed by question 4 from the BASDAI, was associated with fatigue severity. Thus, it seems there is a substantial overlap with fatigue between certain clinical features such as enthesitis and sex.

The need for early identification and treatment of patients with axSpA led to the development of the ASAS classification criteria[14]. The subset nr-axSpA covers the patients who do not have definite sacroiliac joint changes on pelvic radiographs. It is proposed that AS and nr-axSpA are overlapping but distinct entities[29]. The differing features include female predominance, weaker association with HLA-B27, greater diversity with regard to disease progression, and lower response to treatment among patients with nr-axSpA[29]. In our study, both nr-axSpA and AS showed a similar burden of fatigue regarding frequency and severity. These results are in accordance with a previous study that revealed similar levels of fatigue between AS and nr-axSpA[30].

Anemia of inflammation is a common finding in inflammatory rheumatic diseases, particularly for rheumatoid arthritis. It is reported that nearly 15% of patients with AS have anemia of inflammation[31], which may have potential to contribute fatigue in this population. In our group, nearly 18% of the patients had anemia. Analysis of our group showed that the percentages of patients with anemia were similar between the severe and low fatigue groups. In addition, neither correlation nor regression analysis showed an association between anemia and fatigue severity.

We investigated the effect of biologic drug use on fatigue. When compared with the baseline values, there were significant reductions in terms of fatigue obtained from the FSS and BASDAI Q1. Reductions in fatigue levels were also accompanied by decreasing levels of total BASDAI and the mean of BASDAI Q5 and Q6. In addition, TNFi therapy resulted in a 50% decrease in the number of patients with active disease. The number of total patients with severe fatigue decreased nearly 20% after biological treatment. It was also

of note that there are still a considerable number of patients with severe fatigue after biologic therapy. Our results are in accordance with the findings of a study conducted in patients with AS[32]. In that study, there were 39 patients who had baseline and followup data. According to their findings, 52% of the patients still had significant fatigue after TNFi[32]. In our study, despite the decreasing fatigue levels with anti-TNF treatment, there was no association between biologic therapy and fatigue severity. The latter finding may suggest that the beneficial effect of TNFi therapy on fatigue may have an indirect effect through the improvement of other accompanying variables such as the health status improvement.

We also studied several QoL measures including SF-36 MCS, SF-36 PCS, ASQoL, EQ-5D, and HAQ. We found that all these indices were impaired in the patients with severe fatigue. In addition, these variables showed moderate associations with fatigue severity. Notably, we showed that the strongest predictor on severe fatigue was the HAQ score. Our results suggest that impaired QoL is closely allied with worse fatigue, as has been observed previously[1,2,12,27,33,34].

Fatigue is a common symptom in axSpA and is influenced by a combination of several factors. The burden of fatigue among patients with nr-axSpA is similar to that seen in patients with AS. While biologics are effective in reducing disease activity in most patients with axSpA, their effect on fatigue is rather limited. In axSpA, fatigue remains unresponsive to TNFi in nearly 80% of patients. Thus, targeted therapies for fatigue should be explored as an important research priority.

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