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Medicine

Assessment of Association between Fatigue and Disease Activity in Axial Spondyloarthritis

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Abstract	Original Research Article

Introduction: Spondyloarthritis (SpA) is a common disease characterised by chronic inflammatory pain and debilitating manifesting itself most often in stiffness. Fatigue is widely regarded as a cardinal manifestation of Axial SpA and is one of the three most frequently reported symptoms alongside pain and stiffness. This study sought to assess the association between fatigue and disease activity in axial spondyloarthritis. *Aim of the study:* The aim of this study is to assess the association between fatigue and disease activity in axial spondyloarthritis. *Methods:* This cross-sectional study was conducted at the Department of Physical Medicine & Rehabilitation, BSMMU, from October 2021 to September 2022. A total of 48 patients fulfilling the ASAS criteria for Axial SpA were included. Data were collected through structured interviews, assessing socio-demographic parameters and disease history. Fatigue severity was measured using the FSS, and disease activity was evaluated with the ASDAS-CRP. Statistical analysis was performed using SPSS 24. *Result:* The majority of the studied patients (70.8%) had a normal BMI. The mean FSS score was significantly higher for patients with high and very high disease activity compared to those with inactive and low disease activity ($p < 0.05$). A significant association was found between disease activity and fatigue severity ($p < 0.05$). There is a statistically significant positive correlation between disease activity and fatigue severity ($p < 0.05$). A significant positive correlation was observed between the ASDAS-CRP score and the FSS score ($r = +0.479$, $p = 0.001$). *Conclusion:* Study results found that fatigue severity and disease activity score had significant positive linear association. Hence, it can be concluded that fatigue and disease activity have significant relationship in axial spondyloarthritis. Further large-scale multicenter research is warranted.
Keywords: Axial Spondyloarthritis (Axial SpA), Fatigue Severity Scale (FSS), Disease Activity, ASAS, ASDAS-CRP.

I INTRODUCTION

Spondyloarthritis (SpA) is a common disease characterised by chronic inflammatory pain and debilitating manifesting itself most often in stiffness. It affects 0.5%–2% of the global population [1]. Axial SpA prevalence estimates range widely both in developed and developing countries, from 0.03% to 2.5% [2]. The regional pooled prevalence of Axial SpA around the world was estimated to range from 0.20% in South-East Asia [3]. The Assessment of Spondyloarthritis International Society (ASAS) classification criteria defines the clinical manifestations of SpA as axial, peripheral, and extra-articular [4].

Pain is the most frequent symptom in Axial SpA, particularly in early stages, and part of the tools of disease activity evaluation (ASDAS: Ankylosing Spondylitis Disease Activity Score). The disease activity is related to frequency and severity of fatigue. Inflammation, pain are associated with greater fatigue, but other factors, such as physical inactivity, sleep

disturbance and depression, explain the major differences in fatigue.

Fatigue is described as extreme tiredness, typically resulting from mental or physical exertion or illness [5]. It negatively impacts patients physical functioning and relationships daily working lives, and sport and leisure activities. It is widely regarded as a cardinal manifestation of Axial SpA and is one of the three most frequently reported symptoms alongside pain and stiffness [6]. Despite the advent of biologics, fatigue remains poorly treated in many, thus highlighting its complexity and the management challenge it poses. Current understanding holds that fatigue in spondyloarthritis is multi-factorial and associated with disease-specific parameters, poor psychological health, sleep disturbance and women gender with disease activity being the single most important predictor [7]. Fatigue is frequently reported by patients with Axial SpA and it is defined as a subjective sensation of generalized weariness together with a mental component [8]. It is considered a multidimensional and complex phenomenon and is found to be associated with pain and low physical activity [9].

Fatigue will be assessd by according to the Fatigue Severity Scale (FSS) which has acceptable reliability, internal consistency, sensitivity and responsiveness for people with neurological and rheumatological diseases.

FSS total scores are usaually reported as the mean score over the nine items; a higher score indicates greater severity. Fatigue is a common problem in patients with SpA and can be as disabling as pain, is difficult to manage, and has a substantial impact on quality of life. Considering this, the purpose of this study was to assess the association between fatigue and disease activity in axial spondyloarthritis.

II OBJECTIVES
- The aim of this study is to assess the association between fatigue and disease activity in axial spondyloarthritis.

III METHODOLOGY & MATERIALS
This cross-sectional study was conducted at the Department of Physical Medicine & Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU), over a period from October 2021 to September 2022. A total of 48 patients fulfilling the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for Axial SpA were included in the study. Inclusion criteria encompassed individuals aged 18 years or older, diagnosed with Axial SpA, and willing to participate. Exclusion criteria excluded patients with known neuropsychiatric disorder, e.g. Schizophrenia, Psychosis, Anxiety disorder, Mood disorder etc., cognitive dysfunction, infectious diseases, malignancy such as lymphoma, multiple myeloma etc, Pregnancy, Co-morbidities such as Diabetes mellitus, Hypertension, Bronchial Asthma, End stage renal disease and certain chronic diseases. Data were collected through structured interviews covering socio-demographic parameters, disease history, co-morbidities and laboratory profiles. Fatigue severity was assessed using the fatigue severity scale (FSS), while disease activity was evaluated using the Ankylosing Spondylitis Disease Activity Score based on C-reactive protein (ASDAS-CRP). Statistical analysis was conducted using SPSS 24, employing descriptive and inferential statistical methods such as chi-square test, one-way ANOVA test, and Pearson's correlation coefficient test. p-value less than 0.05 was considered as statistically significant. Ethical clearance was obtained from the institutional review board, and informed written consent was obtained from all participants to ensure confidentiality throughout the study.

IV RESULT

Table 1: Demographic variables of the study patients (N=48)

Variables		No. of patients (n)	Percentage (%)
Age (in years)	20-29	13	27.10
	30-39	21	43.80
	40-49	8	16.60
	50-59	5	10.40
	≥60	1	2.10
Gender	Male	32	66.70
	Female	16	33.30
Education	Bachelor or above	9	18.75
	Secondary	20	41.70
	Primary	13	27.00
	Higher Secondary	6	12.50
Occupation	Unemployed	3	6.20
	Service	7	14.60
	Business	13	27.00
	Day labor	4	8.33

Variables		No. of patients (n)	Percentage (%)
	Housewife	14	29.10
	Student	7	14.60
Socio-economic status	Lower-middle income	21	44.00
	Lower income	20	42.00
	Upper-middle income	4	8.00
	High income	3	6.00
BMI (in kg/m^2)	Height (in cm)		164.10±7.15
	Weight (in kg)		63.77±7.99
	BMI (in kg/m^2)		23.71±2.85
	BMI category		
	Normal	34	70.80
	Overweight	14	29.20

The mean age (in years) for the studied patients was 36.67±10.01 (SD) years and the majority of the studied patients (43.8%) belonged to 30-39 years of age. The majority of the studied patients (66.7%) were male. Regarding educational status, the majority (41.7%) completed their education up to SSC followed by decreasing order completed primary (27.0%), completed HSC (12.5%), Bachelor or above (18.7%). In terms of occupation, the majority were Housewife (29.1%) followed by decreasing order Businessman (27.0%), Student (14.6%), Service (14.6%), and Day labor (8.3%), Unemployed/ retired (6.2%). The majority of the studied patients (44%) belonged to lower-middle income family followed by decreasing order lower income family (42%), upper-middle income family (8%) and high income (6%). The mean BMI (in kg/m^2) was 23.71±2.85 (SD) for the studied patients and the majority of the studied patients (70.8%) were with normal BMI and 29.2% were overweight.

Table 2: Association of fatigue severity score with the disaese activity (n=48)

FSS	Disease activity				p-value
	Inactive	Low disease activity	High disease activity	Very high disease activity	
Mean±SD	3.46±1.53	3.65±1.07	5.13±0.89^{αβ}	5.78±1.56^{ab}	<0.001

The mean FSS was significantly different according to disease activity category (p<0.05). The mean FSS score was significantly more for the patients with high and very high disease activity than the patients with inactive and low disease activity. But no significant FSS difference was seen among patients with inactive and low disease activity.

Table 3: Association of disease activity and fatigue of the study patients (n=48)

Disease activity	Fatigue Severity		p-value
	Low (≤5)	High (>5)	
	n (%)	n (%)	
Inactive (<1.3)	8 (80.0)	2 (20.0)	<0.001
Low disease activity (<2.1)	15 (88.2)	2 (11.8)	
High disease activity (>2.1)	3 (21.4)	11 (78.6)	
Very high disease activity (>3.5)	2 (28.6)	5 (71.4)	

Patients with inactive disease, 80.0% of them had low FSS and 20.0% had high FSS, 88.2% of the patients with low disease activity had low FSS and 11.8% had high FSS. Besides, patients with high disease activity, 21.4% of them had low FSS and 78.6% had high FSS. And, patients with very high disease activity, 28.6% had low FSS and 71.4% had high FSS. A significant association was seen among disease activity and fatigue severity (p<0.05).
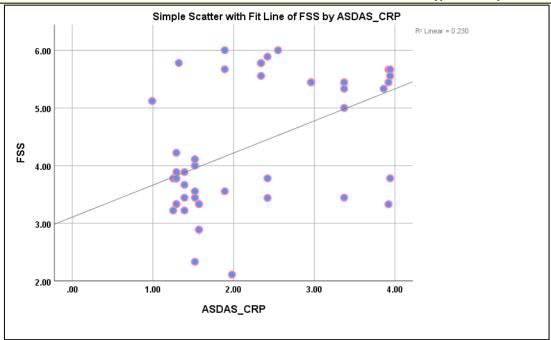
Figure 1: Scatter diagram showing the correlation among disease activity score and fatigue severity score (N=48)

Scattered plot showing a significant positive correlation (r=+0.479, p=0.001) among ASDAS-CRP score and FSS score.

Table 4: Correlation among disease activity (ASDAS-CRP) score and fatigue severity score (N=48)

	Correlation coefficient (r)	p-value
ASDAS-CRP	0.479	0.001

The table shows that there is a statistically significant (P <0.05) positive correlation between disease activity and fatigue severity.

V DISCUSSION

Fatigue is defined as a subjective sensation of generalized weariness together with a mental component [10]. In healthy individuals, it is temporary, whereas, in rheumatologic patients, fatigue can be continuous and persistent despite appropriate daily rest. Further fatigue is one of the most important symptoms of spondyloarthritis, together with pain and stiffness. This manifestation has not been widely studied, probably because it is a multifactorial, subjective symptom and it is difficult to quantify. However, fatigue was also associated with disease activity [8]. In this study, 48 patients with axial spondyloarthritis were included and this study aimed to assess the association between fatigue and disease activity in axial spondyloarthritis.

In this present study, the mean age (in years) for the studied patients was 36.67±10.01(SD) years and the majority of the studied patients (43.8%) belonged to 30-39 years of age and two-thirds of the patients were male. A similar study showed that the mean age was 47.73±13.26 (SD) years and 68.68% of patients were male [8]. Regarding educational status, the majority (41.7%) of the studied patients in this current study completed their education up to SSC followed by decreasing order completed primary (27.0%), completed HSC (12.5%), bachelor or above (18.7%) and in terms of occupation, the majority were housewife (29.1%) followed by decreasing order businessman (27.0%), student (14.6%), service (14.6%) day labor (8.3%) and unemployed/ retired (6.2%). Another similar study showed that 42% completed secondary level education and 60% of the studied patients were working persons [11]. Also, the majority of the studied patients (44%) belonged to lower-middle income families followed by decreasing order lower income families (42%), upper-middle income family (8%), and high income (6%). The mean BMI (in kg/m^2) was 23.71±2.85 (SD) for the studied patients and although the majority of the studied patients (70.8%) were with normal BMI a large number of patients (29.2%) were overweight. A study showed that disease activity measures in spondyloarthritis were influenced by BMI and the relative risk was higher for obese and overweight people [12].

The mean FSS was significantly different according to disease activity category (p<0.05). It was seen that the FSS score was increased with the disease severity and the mean FSS score was significantly more for the patients with high and very high disease activity than the patients with inactive and low disease activity. But no significant FSS difference was seen among

patients with inactive and low disease activity. In patients with inactive disease, 80% of them had low FSS and 20% had high FSS, 88.2% of the patients with low disease activity had low FSS and 11.8% had high FSS. Besides, in patients with high disease activity, 21.4% of them had low FSS and 78.6% had high FSS. And, in patients with very high disease activity, 28.6% had low FSS and 71.4% had high FSS. This study found a significant association between disease activity and fatigue (p<0.05). ASDAS-CRP score and FSS score were significantly positively correlated in this study which means those who had more disease activity scores had more FSS score. Another similar study showed that according to BASDAI-fatigue criteria 55.3% of the total axial spondyloarthritis patients had severe fatigue and 31.1% had severe fatigue according to SF-36 VT criteria and they also found that patients who experienced severe fatigue generally reported higher disease activity and greater perceived disease impact [13]. So, disease activity assessments stood out as a key predictor of fatigue among the patients with axial spondyloarthritis in this present study. Some other studies also found disease activity as a well-recognized driver of fatigue [9,14].

So, in this study, a significant association was seen between the disease activity and fatigue. Also, it was seen that fatigue severity score was significantly higher for the patients with high and very high disease activity than the patients with inactive and low disease activity. This study was a single-centered study with a small sample size so this study may not represent the whole scenario. A more multicentered study with large sample size is recommended to corroborate these research findings.

Limitations of the study
This study had some limitations.
- All samples were collected from a single site
- Sample size was small
- Sample was taken purposively, so randomization was not done

VI CONCLUSION
As there are no conclusive physiological and biochemical markers, accurate assessment relies on validated self-reporting measures for fatigue and disease activity in axial spondyloarthritis patients. This study assessed the association between fatigue and disease activity in axial spondyloarthritis. Study results found that fatigue severity and disease activity score had significant positive linear association. Very high disease activity patients had the highest fatigue severity while inactive disease had the least fatigue severity. Hence, it can be concluded that fatigue and disease activity have significant relationship in axial spondyloarthritis. Further large-scale multicenter research is warranted.

REFERENCES
1. Allado, E., Moussu, A., Bigna, J. J., Hamroun, S., Camier, A., Chenuel, B., & Hamroun, A. (2020). Global prevalence of spondyloarthritis in low-income and middle-income countries: a systematic review and meta-analysis protocol. *BMJ open*, *10*(10), e041180.
2. Zlatković-Švenda, M. I., Stojanović, R. M., Šipetić-Grujičić, S. B., Radak-Perović, M. M., & Guillemin, F. (2019). Prevalence of spondyloarthritis and its subtypes-are they really comparable?. *Srpski arhiv za celokupno lekarstvo*, *147*(3-4), 235-242.
3. Stolwijk, C., van Onna, M., Boonen, A. & van Tubergen, A., (2015). Arthritis Care & Research Global prevalence of Spondyloarthritis: A Systematic review and Meta-Regression analysis Running title: Prevalence of SpA Authors: Carmen Stolwijk , MD , PhD Marloes van Onna , MD Annelies Boonen , MD , PhD Astrid van Tub. *Arthritis Care & Research*, 1–27.
4. Citera, G., Bautista-Molano, W., Peláez-Ballestas, I., Azevedo, V. F., Perich, R. A., Méndez-Rodríguez, J. A., ... & Borlenghi, C. E. (2021). Prevalence, demographics, and clinical characteristics of Latin American patients with spondyloarthritis. *Advances in Rheumatology*, *61*.
5. Pilgaard, T., Hagelund, L., Stallknecht, S. E., Jensen, H. H., & Esbensen, B. A. (2019). Severity of fatigue in people with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis–results of a cross-sectional study. *PloS one*, *14*(6), e0218831.
6. Khallaf, M. K., AlSergany, M. A., El-Saadany, H. M., El-Hawa, M. A. A., & Ahmed, R. A. (2020). Assessment of fatigue and functional impairment in patients with rheumatic diseases. *The Egyptian Rheumatologist*, *42*(1), 51-56.
7. Lim, W. Z., Fong, W., Kwan, Y. H., & Leung, Y. Y. (2021). Exploring the prevalence and factors associated with fatigue in axial spondyloarthritis in an Asian cohort in Singapore. *Frontiers in Medicine*, *8*, 603941.
8. López-Medina, C., Schiotis, R. E., Font-Ugalde, P., Castro-Villegas, M. C., Calvo-Gutiérrez, J., Ortega-Castro, R., ... & REGISPONSER Working Group. (2016). Assessment of fatigue in spondyloarthritis and its association with disease activity. *The Journal of Rheumatology*, *43*(4), 751-757.
9. Esbensen, B. A., Stallknecht, S. E., Madsen, M. E., Hagelund, L., & Pilgaard, T. (2020). Correlations of fatigue in Danish patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. *PloS one*, *15*(8), e0237117.
10. Chauffier, K., Paternotte, S., Burki, V., Durnez, A., Elhai, M., Koumakis, E., ... & Gossec, L. (2013). Fatigue in spondyloarthritis: a marker of disease activity. A cross-sectional study of 266 patients. *Clin Exp Rheumatol*, *31*(6), 864-870.
11. Connolly, D., Fitzpatrick, C. & O'Shea, F., (2019). Disease Activity, Occupational Participation, and

Quality of Life for Individuals with and without Severe Fatigue in Ankylosing Spondylitis. *Occupational Therapy International*, 2019.

12. Ortolan, A., Lorenzin, M., Felicetti, M., & Ramonda, R. (2021). Do obesity and overweight influence disease activity measures in axial spondyloarthritis? A systematic review and meta-analysis. *Arthritis Care & Research*, *73*(12), 1815-1825.

13. Lim, W.Z., Fong, W., Kwan, Y.H. & Leung, Y.Y., (2021). Exploring the Prevalence and Factors Associated with Fatigue in Axial Spondyloarthritis in an Asian Cohort in Singapore. *Frontiers in Medicine*, 8(February), 1–9.

14. Gossec, L., Dougados, M., Agostino, M.D. & Fautrel, B., (2015). Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort. *Joint Bone Spine*.