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Are TNF-α and IL-1β Independently Associated with Depression in Axial Spondyloarthritis Patients? A Case-Control Study

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Abstract: Objectives: The aim of this study was to investigate whether serum TNF-α and IL-1β levels are independent risk factors for depression in axSpA patients. Methods: All axSpA patients with BASDAI ≥4 were invited consecutively between March 2021 and August 2021 to participate. Depression was evaluated with the WHO-5 Well-Being scale. Disease activity was assessed using BASDAI (0–10), ASDAS-CRP (0.61–7.22), ASDAS-ESR (0.29–7.61), and health status by ASAS-HI (0–17). Serum TNF-α and IL-1β levels were measured by ELISA. An association between depression and cytokine levels was investigated with Spearman's rank correlation coefficient test. Results: A total of 252 axSpA patients (155 men) could be included; of these, 123 (48.81%) were depressed, and of these, 75 were male. Serum TNF-α and IL-1β were not significantly associated with depression (r −0.041 and 0.110, respectively). Serum TNF-α levels were higher in depressed female axSpA patients (20.05 vs. 17.87; $p = 0.03$). Differences between depressed and non-depressed patients were respectively: TNF-α (19.7 vs.18.0; $p = 0.84$), IL-1β (32.3 vs. 21.2; $p = 0.04$), BASDAI (5.47 vs. 4.77; $p = 0.000$), ASDAS-CRP (4.17 vs. 3.78; $p = 0.000$), ASDAS-ESR (3.86 vs. 3.39; $p = 0.000$), CRP (48.43 vs. 37.93 mg/L; $p = 0.000$), and ASAS-HI (13.37 vs. 10.24; $p = 0.000$). Factors associated with depression were: peripheral joint involvement (OR = 1.073, 95% CI 1.012–1.138), BASDAI (OR = 1.534, 95% CI 1.011–2.335), and ASAS-HI (OR = 1.39, 95% CI 1.239–1.557). Only in depressed patients with peripheral SPA were higher IL-1β levels found, though the differences were probably not clinically relevant. Conclusions: Serum TNF-α and IL-1β were not independently related to depression in axSpA patients. Disease activity, peripheral joint involvement, and reduced health status showed the highest association with depression.

Keywords: AxSpA; depression; risk factors; cytokines (TNF-α and IL-1β)

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1. Introduction

In the general population, depression is a common mental health disorder worldwide, with a prevalence rate of around 5% among adults [1]. In depressed people, several cytokines such as TNF-α, IL-1β, IL-6, IL-10, IL-12, IL-13, and IL-18 were found to be elevated, and IFN-γ decreased [2–9]. In the general population, TNF-α and IL-1β have a pathologic role in depression [6–8]. Risk factors for a higher prevalence of depression are female gender, substance abuse, stress, poor nutrition, adverse childhood experience, sleep disorders, maternal depression, family disharmony, social isolation, low family

income, and also genetics can play a role [10–12]. The prevalence of depression in axial Spondyloarthritis (axSpA) patients ranges from 11 to 64% depending on the questionnaires used, as shown in a meta-analysis [13]. The prevalence rate of depression in axSpA patients in Bangladesh was 61.8% in a pilot study [14]. Possible reasons for a higher prevalence of depression in axSpA patients may be increased disease activity, poor health status, and disease-related impairments [13]. The clinical trials have shown an improvement in depressive symptoms by using TNF-alfa inhibitors in both depressed patients without axSpA with high proinflammatory cytokines [15] and depressed axSpA patients. [16–20]. Serum TNF-α levels were strongly related to the disease activity of axSpA patients [21–24], and IL-1β was also related to disease activity in axSpA patients [22,24]. For both patients and clinicians, it is important to know whether higher values of TNF-α and/or IL-1β might be related to depression in axSpA patients. If that were the case, it could have clinical consequences in the management of depressed axSpA patients. To the best of our knowledge, no studies have looked at a possible association of depression with cytokine levels (TNF-α and IL-1β) among axSpA patients.

Based on the observed high prevalence of depression in axSpA, it was hypothesized that patients with active axSpA with high serum TNF-α and IL-1β levels were more depressed. This study aimed to look for the prevalence of depression in AxSpA patients and a possible association between cytokines (TNF-α and IL-1β) and depression. We also aimed to find out whether serum TNF-α and IL-1β levels are independent risk factors for depression in axSpA patients.

2. Materials and Methods

2.1. Study Design

This study was conducted in the outpatient department of the Department of Rheumatology, Microbiology, and Immunology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. This study was conducted from March 2021 to August 2021.

2.2. Sample Selection

All axSpA patients ≥18 years of age with a BASDAI score ≥4 were invited consecutively and enrolled between March 2021 and August 2021. The axSpa, with or without radiographic sacroillitis, was defined following Rudwaleit et al. [25]. Excluded were patients using biologics and/or prednisolone, as biologics may alter the level of serum cytokines and prednisolone directly causes depression. Patients taking antidepressants were excluded as antidepressant drugs may change the level of cytokines [26].

All patients underwent physical examinations on the same day as the questionnaires were filled out and the laboratory measures and X-rays were performed. The comorbidities like psoriasis, ulcerative colitis, Crohn's disease, and (acute) anterior uveitis were also recorded. Enthesitis was measured with the MASES (Maastricht Ankylosing Spondylitis Enthesitis Score, range 0–13) [27].

We used the overweight range according to the Asian BMI cut-off.

All patients filled out the questionnaires; if they were not able to read, they were assisted by the researcher.

The sample size of 252 was calculated following Zhao et al. [13].

2.3. Supplementary Indices

2.3.1. Disease Activity Was Measured with the following Tools

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). This tool consists of a 0–10 scale (0 being no problem and 10 being the worst problem), which is used to answer 6 questions pertaining to 5 major symptoms of AS. The index results in a final 0–10 BASDAI score. The peripheral joint involvement was self-declared by the patients in the BASDAI questionnaire. If any patients failed to understand the questions, they were explained by the attending physician. The Bangla-translated and validated version of BASDAI was used in this study for measuring the disease activity of this study subjects [28].

The Ankylosing Spondylitis Disease Activity Score (ASDAS). This scale combines BAS-DAI questions on patient-reported outcomes about back pain (1), peripheral pain/swelling (2), and duration of morning stiffness (3), and the "patient's global assessment of disease activity" (4), with either the ESR (ASDAS-ESR) or the CRP (ASDAS-CRP) (5) in a weighted manner. The Bangla version of ASDAS was used for measuring disease activity in this study [29].

2.3.2. Functioning (Health Status)

The ASAS-HI, a health index based on the international classification of functioning, disability, and health (ICF) core set, was developed for patients with AS. This index forms a unidimensional scale, providing a sum score representing a wide spectrum of different levels of functioning [30–34]. The pilot Bangla version of ASAS-HI was used in this study [35].

2.3.3. Depression

The WHO-5 well-being scale (WHO-5) is a short scale with only 5 items.

1. I have felt cheerful and in good spirits.
2. I have felt calm and relaxed.
3. I have felt active and vigorous.
4. I woke up feeling fresh and rested.
5. My daily life has been filled with things that interest me.

Each is scored 5–0.

The WHO-5 has adequate validity both as a screening tool for depression and as an outcome measure in clinical trials, and it has been applied successfully across a wide range of study fields [36]. The score ranges from 0 to 100, with 0 representing the worst imaginable well-being and 100 representing the best imaginable well-being. A cut-off of 50 or less is suggestive of depression [36]. The WHO-5 showed a very high negative association with self- and observer-rated measures of depressive symptoms. It is an easily applicable screening tool for depression that has high sensitivity (93%) and specificity (83%) for depression according to the DSM IV criteria [36]. The WHO-5 has been translated into over 30 languages and applied in studies all over the world.

The WHO-5 has shown adequate validity both as a screening tool for depression and as an outcome measure in clinical trials [36]. The pilot Bangla version of the WHO-5 well-being scale was used in this study [37]. This was the main screening measure for depression.

2.4. Laboratory Tests

The CRP, ESR, and levels of TNF-α and IL-1β were measured. As the HLA B27 test is an expensive investigation in our country, we studied whether the patients fulfilled the ASAS criteria of axSpA. When no definite sacro-iliitis had been found on the X-rays, a HLA B27 test was carried out.

Study Kits and Sample Preservation

Commercially available kits (DRG Instruments GMBH, Marbur, Germany, distributed by DRG International, Springfield, NJ, USA. TNF-α ELISA EIA 4641 and IL-1β ELISA EIA 4437) were used for the measurement of serum TNF-α and IL-1β levels by the ELISA method following the manufacturer's instructions. The lower limit of detection of TNF-α and IL-1β was 0.7 pg/mL and 0.35 pg/mL, respectively (no upper limit was given by Brand Inc.). No standard normal values of serum IL-1β and TNF-α are available either, as the values of 'normal' serum levels of IL-1β and TNF-α among healthy controls vary in a wide range among different studies. This means that we cannot compare the 'normal' values of depressed and non-depressed patients.

All kits were preserved at 2–8 °C. Five milliliters of peripheral blood were drawn through venipuncture from the antecubital veins in all subjects. Serum was obtained by

centrifugation (3000 rpm for 15 min), and separated sera were kept in aliquots at −20 °C until the time of the assay for a maximum of 2 months.

X-rays: Routine AP radiographs of SI joints were performed in all patients.

2.5. Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA: IBM Corp., 2019. Descriptive statistics (number, percentage, and mean) were used for demographic and other qualitative data. The Chi-square test (for education) and Mann–Whitney U test (for other demographic, clinical, and laboratory variables) were used to compare depressed and non-depressed groups. Spearman's rank correlation coefficient test was used to determine the association between the score of depression and the serum values of TNF-α and IL-1β.

At first, we used the Kolmogorov–Smirnov test for testing normality. Then, for the variables, we used the non-parametric test, and for those that are not normally distributed, we used the parametric—*t* test for those who are normally distributed.

The odds ratio of factors at a 95% confidence interval related to depression was determined by the univariate and multiple logistic regression analyses. A p-value < 0.05 was considered significant.

The important clinical variables, which are significant at $\alpha = 0.05$ levels in a bivariate analysis, were included in a multiple logistic regression analysis with a forward selection procedure.

In this study, we made 32 comparisons and tests; since these are all from the same subjects, the used variables may not be independent. Therefore, we applied Bonferroni's correction to avoid spurious and significant differences.

2.6. Ethical Implications

This research protocol was approved by the Institutional Review Board, BSMMU (BSMMU/2021/2199) prior to the commencement of this study. This research was performed according to the principles of the Declaration of Helsinki. The aims and objectives of this study, along with its procedure, risks, and benefits, were explained to the patients and informed written consent was obtained from each patient before enrollment. Privacy, anonymity, and confidentiality were strictly maintained. Only the investigator and guide had access to the data, except for law-enforcing persons in special circumstances. Data might be exposed abroad for academic purposes only while maintaining anonymity. Every patient enjoyed the right to participate and/or withdraw from this study at any time. The withdrawal from this study did not deprive the patients of their deserved medical services. This study was free from any economic benefits or influences. The Bangla version of the BASDAI, ASDAS, ASAS-HI, and WHO-5 well-being scales was used in this study with permission from the principal author.

3. Results

All axSpA patients were invited between March 2021 and August 2021. A total of 252 consecutive axSpA subjects with BASDAI scores ≥ 4 could be enrolled out of these 155 men. Almost all patients, 247 (98.0%), were taking NSAIDs. As DMARDs, they had sulfasalazine 162 (64.3%), methotrexate 26 (10.3%), and leflunomide 1 (0.4%).

Of the patients, almost half of 123 (48.81%) were depressed; according to the WHO-5 well-being scale, 75 of these were male. The demographic and clinical characteristics of this study subjects with and without depression are summarized in Tables 1 and 2, respectively.

The axSpA patients with higher education were less often depressed ($p < 0.001$), while those with lower educational status (class 6 to 10) were more often depressed ($p = 0.02$). (Table 1)

In further demographic and clinical variables, no significant differences were observed between depressed and non-depressed patients regarding age, gender, marital status, monthly income, BMI, residence, occupation, tobacco use, and disease duration (Tables 1 and 2).

Table 1. Demographic characteristics of the axSpA patients with and without depression (n = 252).

Characteristics		Depression (n = 123)	No Depression (n = 129)	*p*-Value
		Number (%)/ (Mean ± SD)	Number (%)/ (Mean ± SD)	
Age		34.30 ± 9.38	33.88 ± 11.750	0.411
Monthly income		30487.80 ± 17,595.35	29767.44 ± 14,880.52	0.956 †
BMI		24.83 ± 3.23	24.90 ± 3.77	0.643 †
Gender	Male	75 (48.4)	80 (51.6)	0.87 *
	Female	48 (49.5)	49 (50.5)	
Residence	Rural	42 (51.2)	40 (48.8)	0.60 *
	Urban	81 (47.6)	89 (52.4)	
Education	No to primary	27 (46.6)	31 (53.4)	0.58 *
	Up to Secondary	50 (59.5)	34 (40.5)	0.02 *
	Higher secondary and above	46 (41.8)	64 (58.2)	0.00 *
Occupation	Student	14 (40.0)	21 (60.0)	0.348 *
	Housewife	43 (49.4)	44 (50.6)	
	Business	16 (50.0)	16 (50.0)	
	Service	41 (47.7)	45 (52.3)	
	Others £	9 (75.0)	3 (25.0)	
Marital status	Married	29 (42.6)	39 (57.4)	0.102 *
	Unmarried	92 (52.6)	83 (47.4)	
	Others €	2 (22.2)	7 (77.8)	
Current tobacco use	Yes	10 (37.0)	17 (63.0)	0.20 *
	No	113 (50.2)	112 (49.8)	

n = number, SD = Standard Deviation, * *p* value based on Chi-square test, † *p* value based on Mann–Whitney U test, others £ (unemployed, cultivator, and retired), others € (widow and divorce).

Table 2. Clinico-laboratory characteristics of this study subjects with and without depression (n = 252).

Characteristics		Depression (n = 123)	No Depression (n = 129)	*p*-Value
		(Mean ± SD) (%)	(Mean ± SD) (%)	
Disease duration (Year)		7.21 ± 6.35	7.75 ± 7.74	0.49 †
Number of joints involved		7.20 ± 8.75	3.45 ± 4.25	0.000 †
Enthesitis (%)	Yes	54 (55.7)	43 (44.3)	0.08 *
	No	69 (44.5)	86 (55.5)	
MASES		2.20 ± 3.13	1.46 ± 2.72	0.05 †
Uveitis	Yes	13 (48.1)	14 (51.9)	0.94 *
	No	110 (48.9)	115 (51.1)	
Dactylitis	Yes	2 (50)	2 (50)	1.00 §
	No	121 (48.8)	127 (51.2)	

Table 2. *Cont.*

Characteristics		Depression (n = 123) (Mean ± SD) (%)	No Depression (n = 129) (Mean ± SD) (%)	*p*-Value
Psoriasis	Yes	1 (16.7)	5 (83.3)	0.21 §
	No	122 (49.6)	124 (50.4)	
Bloody diarrhea	Yes	2 (50.0)	2 (50.0)	1.00 §
	No	121 (48.8)	127 (51.2)	
Urethral discharge	Yes	1 (33.3)	2 (66.7)	1.00 §
	No	122 (49.0)	127 (51.0)	
Family history of SpA	Yes	53 (47.7)	58 (52.3)	0.77 *
	No	70 (49.6)	71 (50.4)	
HLA B27pos		84 (50.9)	81 (49.1)	0.29 †
HLA B27 neg		9 (60.0)	6 (40.0)	
HLA B27 not tested		30 (41.7)	42 (58.3)	
		Median	Median	
BASDAI		5.2	4.7	0.000 †
ASDAS-ESR		3.7	3.4	0.000 †
ASDAS-CRP		4.17 ± 0.77	3.78 ± 0.73	0.000 ††
ASAS-HI		14	10.24	0.000 †
WHO-5 well-being score		28	68	0.000 †
ESR		35	29	0.00 †
CRP		33.8	25.29	0.00 †
TNF-α value		19.7	18.0	0.840 †
IL-1β value		32.3	21.2	0.040 †
TNF-α value men		15.6	14.95	0.936 †
TNF-α value women		20.05	17.87	0.030 †
IL-1β value in men		17.6	7.83	0.600 †
IL-1β value in women		14.60	0.00	0.588 †

n = Number, % = Percent, SD = Standard Deviation, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, ESR = Erythrocyte Sedimentation Rate, CRP = C-reactive Protein, ASAS-HI = Ankylosing Spondyloarthritis International Society Health Index, TNF-α = Tumor Necrosis Factor-alpha, IL-1β = Interleukin-1 beta, * *p* value based on Chi square test, § *p* value based on Fisher exact test, † *p* value based on Mann–Whitney U test, †† *t* test.

The mean BMI of our study was within the overweight (4 underweight and 62 overweight) range according to the Asian BMI cut-off.

Only 27 subjects (10.7%) were current smokers in our study, and we found no relation between depression and smoking.

No significant differences were found regarding enthesitis (MASES score), uveitis, dactylitis, psoriasis, bloody diarrhea, urethral discharge, or family history of SpA (Table 2).

Between depressed and non-depressed patients, no significant differences were found regarding serum TNF-α (19.7 vs.18.0; $p = 0.84$) or serum IL-1β (32.3 vs. 21.2; $p = 0.04$) (Table 2).

On the other hand, highly significant differences were found regarding BASDAI (median 5.2 vs. 4.7; $p = 0.000$), ASDAS-CRP (4.17 vs. 3.78; $p = 0.000$), ASDAS-ESR (median

3.7 vs. 3.4; $p = 0.000$), CRP (median 33.8 vs. 25.29 mg/L; $p = 0.001$), and ASAS-HI (median 14 vs. 10.24; $p = 0.000$), respectively (Table 2).

After applying Bonferroni's criterion, the variables: education, number of joints involved, BASDAI, ASDAS-ESR, ASDAS-CRP, ASAS-HI, WHO-5 well-being score, ESR, and CRP demonstrate significant differences between depressed and non-depressed patients.

Out of 252, 201 (79.76%) of the axSpA patients had peripheral involvement (Table 3).

Depressed patients with pure axSpA had only significantly higher ASDAS-CRP and CRP (Table 3).

Depressed patients with peripheral involvement had significantly higher numbers of involved joints: BASDAI, ASDAS-CRP, ASDAS-ESR, ASDAS-HI, CRP, and also IL-1β (Table 4). As this was the largest subgroup, it could be expected that these figures are comparable with those of the total group (Table 2).

Table 3. Characteristics of pure axSpA patients with and without depression (n = 51).

Variables	Depression (n = 18)	No Depression (n = 33)	*p*-Value
	Number (%)/ (Mean ± SD)	Number (%)/ (Mean ± SD)	
BASDAI	4.64 ± 0.91	4.40 ± 0.45	0.366 †
ASDAS-CRP	4.16 ± 0.72	3.46 ± 0.68	0.001 †
ASDAS-ESR	3.48 ± 0.67	3.11 ± 0.51	0.047 †
ASAS-HI	12.52 ± 2.38	10.78 ± 3.67	0.128 †
ESR	37.68 ± 25.29	28.37 ± 16.78	0.205 †
CRP	57.45 ± 45.90	25.94 ± 22.29	0.002 †
TNF-α	15.82 ± 8.24	18.04 ± 9.14	0.250 †
IL-1β	46.99 ± 112.86	20.68 ± 41.13	0.888 †

† *p* value based on Mann–Whitney U test.

Table 4. Characteristics of axSpA patients with peripheral involvement with and without depression (n = 201).

Variables	Depression (n = 104)	No Depression (n = 97)	*p*-Value
	Number (%)/ (Mean ± SD)	Number (%)/ (Mean ± SD)	
Number of joints involved	8.51 ± 8.9	4.59 ± 4.34	0.001 †
BASDAI	5.62 ± 1.24	4.89 ± 0.82	0.000 †
ASDAS-CRP	4.17 ± 0.78	3.88 ± 0.71	0.012 †
ASDAS-ESR	3.93 ± 0.83	3.48 ± 0.67	0.000 †
ASAS-HI	13.53 ± 2.59	10.06 ± 3.18	0.000 †
ESR	44.98 ± 30.38	32.63 ± 20.55	0.008 †
CRP	46.78 ± 40.48	41.89 ± 44.83	0.116†
TNF-α	20.25 ± 12.62	17.40 ± 8.65	0.427 †
IL-1β	29.52 ± 54.98	21.32 ± 46.45	0.017 †

n = Number, % = Percent, SD = Standard Deviation, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, ESR = Erythrocyte Sedimentation Rate, CRP = C-Reactive Protein; ASAS-HI = Ankylosing Spondyloarthritis International Society Health Index, TNF-α = Tumor Necrosis Factor- alpha, IL-1β = Interleukin-1 beta, † *p* value based on Mann–Whitney U test.

Out of 252 patients, 180 were advised to have a HLA-B27 test performed. Among these 180, 165 (91.67%) were HLA-B27 positive. We also evaluated the relation between depression and HLA B27 positivity and the relation of HLA B27 positivity with cytokine levels, but no relation was found.

When looking at women, the serum TNF-α levels were higher in the depressed women with axSpA (20.05 $\pm$ 11.62 vs. 17.87 $\pm$ 9.20; p = 0.03). But this difference is not clinically relevant, considering the standard deviation (Table 2).

After multiple logistic regression analysis using the forward selection method for model identification, the independent risk factors for depression were axSpA with peripheral joint involvement (OR = 1.073, 95% CI 1.012–1.138), BASDAI (OR = 1.534, 95% CI 1.011–2.335), and ASAS-HI (OR = 1.389, 95% CI 1.239–1.557), as shown in Table 5. These data were not different between male and female patients. The subgroup analysis between depressed and non-depressed women is shown in Table 6.

Table 5. Factors for depression in SpA patients, assessed with multiple logistic regression analysis using forward selection method for model identification.

Variables	p	OR	95% CI for OR	
			Lower	Upper
Education				
Illiterate or primary				
Up to SSC	0.638	1.206	0.553	2.632
HSC and above	0.067	0.509	0.247	1.049
No of peripheral joints affected.	0.019	1.073	1.012	1.138
BASDAI	0.044	1.534	1.011	2.335
ASAS-HI	0.000	1.39	1.239	1.557
ESR	0.111	1.025	0.944	1.054
CRP	0.307	0.992	0.977	1.01
ASDAS-CRP	0.380	1.506	0.604	3.75
ASDAS-ESR	0.518	0.654	0.179	2.375
IL-1β	0.862	0.030	0.994	1.007

SSC = Secondary School Certificate, HSC = Higher Secondary Certificate, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, ESR = Erythrocyte Sedimentation Rate; CRP = C Reactive Protein, ASAS-HI = Ankylosing Spondyloarthritis International Society Health Index, IL-1β = Interleukin-1 beta, OR = Odds Ratio, CI = Confidence Interval, Rounding conducted.

Table 6. Characteristics comparison of the depressed and non-depressed study subjects subgroup analysis within women (n = 97).

Women (n = 97)			
Variables	**Depression (n = 48)**	**No Depression (n = 49)**	***p*-Value**
	Number (%)/ (Mean $\pm$ SD)	**Number (%)/ (Mean $\pm$ SD)**	
Age (years)	36.64 $\pm$ 9.01	36.06 $\pm$ 11.3	0.76 †
Disease duration	6.27 $\pm$ 6	8.14 $\pm$ 8.4	0.68 †
Number of the peripheral joint involvement	8.81 $\pm$ 8.83	4.20 $\pm$ 4.74	0.002 †
MASES	3.15 $\pm$ 3.37	1.51 $\pm$ 2.66	0.001 †
BASDAI score	5.55 $\pm$ 0.99	4.87 $\pm$ 0.80	0.000 †

Table 6. *Cont.*

Women (n = 97)			
Variables	**Depression (n = 48)**	**No Depression (n = 49)**	***p*-Value**
	Number (%)/ (Mean ± SD)	**Number (%)/ (Mean ± SD)**	
ASDAS-CRP score	3.99 ± 0.62	3.61 ± 0.65	0.005 †
ASDAS-ESR score	3.81 ± 0.62	3.42 ± 0.63	0.004 †
ASAS-HI score	13.06 ± 2.89	10.76 ± 2.98	0.001 †
ESR	39.66 ± 22.95	33.24 ± 16.26	1.000 †
CRP	36.36 ± 31.81	24.01 ± 22.13	0.472 †
TNF-α value	20.05 ± 11.62	17.87 ± 9.20	0.030 †
IL-1β value	31.02 ± 67.89	10.74 ± 22.48	0.588 †

n = number, % = percent in parenthesis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, ESR = Erythrocyte Sedimentation Rate, CRP = C-Reactive Protein, ASAS-HI = Ankylosing Spondyloarthritis International Society Health Index, TNF-α = Tumor Necrosis Factor-alpha, IL-1β = Interleukin-1 beta, † *p*-value based on Mann–Whitney U test, Rounding conducted.

The data for TNF-α and IL-1β were not normally distributed. Out of 252 values, 97 IL-1β values were below the detection level (considered as 0 pg/mL according to the manufacturers' instructions). The log transformation failed to bring about a normal distribution. The results were similar with both per-protocol data and transformed data in terms of the association between depression and cytokines (TNF-α and IL-1β). TNF-α and IL-1β were not significantly associated with depression: Spearman's rank correlation coefficients (r) for TNF-α and IL-1β in depressed axSpA patients were −0.041 and 0.110, respectively (Table 7).

Table 7. Spearman's rank correlation coefficient of TNF-α and IL-1β with depression.

Variables	**r**	***p*-Value**
TNF-α	−0.041	0.521
IL-1β	0.110	0.084

4. Discussion

A total of 252 cases of axSpA were enrolled in this case-control study. Out of them, 123 (48.81%) were depressed based on the WHO-5 well-being scale.

In our study, no association was observed between depression and cytokines (serum TNF-α and IL-1β). We did not come across similar types of studies published to assess the association between depression and cytokines (TNF-α and IL-1β) in axSpA patients. In primary depression, both TNF-α and IL-1β may have pathologic roles [6–8]. Despite the fact that an improvement in depressive symptoms was observed by using TNF inhibitors in depressed patients with high proinflammatory cytokines with or without axSpA [15–20].

Among the depressed female axSpA patients, the serum level of TNF-α was found to be significantly higher in our study, although the difference was not clinically relevant. With similar disease activity, the mean TNF-α value was observed to be lower in females than in males axSpA patients [38]. A lower level of TNF-α in women than in men was observed in primary depression [26]. Further large sample sizes or population-based studies are needed to clarify the issue.

In this study, the mean age of the depressed and non-depressed groups was similar, which was comparable with the findings of Baysal et al. [39]. Redeker et al., on the other hand, found a mean lower age to be related to more depression [40], while Park et al. and Shen et al. found a mean higher age-related to more depression [41,42]. In our study, 48.4%

of men and 49.5% of women were depressed, which was consistent with the observation of Parkinson et al. [9]. Women had a higher rate of depression, as found by Wright [38], but Webers et al. found that men were at higher risk for depression [43].

The mean BMI of our study was within the overweight range according to the Asian BMI cut-off. There was no difference in BMI between depressed and non-depressed patients in our study. Others found those with a higher BMI to have a greater chance of depression [44]. But a U-shaped association between BMI and depression was also reported by others, which means that both being underweight and obesity were associated with depression [45].

In our study, subjects with lower educational status (class 6 to 10) were found to be more often depressed (p = 0.02). A similar observation was reported by others [26,46]. Higher educational status was found to be related to less depression by promoting better health [47]; this finding was compatible with our observation.

Only 27 subjects (10.7%) were current smokers in our study, and we found no relationship with depression. The prevalence of smoking among the general population of Bangladesh was 36.35%, higher among men and in older and poorer people [48]. The prevalence of smoking in axSpA patients was 32.8% [49]. Current smoking was found to be a risk factor for depression [44]. The low prevalence of smoking in our study was consistent with the rate of cigarette smoking in the general population in Bangladesh, but not with that among axSpA patients. The explanation for this inconsistency needs to be identified by further study.

In our study, only four participants were divorced and five were widows. No statistically significant difference was found due to the small group of samples. Marital status (being widowed, divorced, or separated) was associated with an increased risk for depression [42]. The prevalence of divorce among the general population in Bangladesh was 0.6–2.7%, depending on different areas [50]. The divorce rate among axSpA patients was 5.6%, which was 2.8% in our study [51]. The observed divorce rate was similar to the divorce rate of the general population. The causes of a lower rate of divorce in our study in comparison to another study in axSpA may be due to family pressure on females against divorce, male dependency, and social customs [50].

The mean disease duration (years) was not significantly different in the depressed group in our study, and a similar observation was found by others [37]. But in a study by López-Medina et al., longer disease duration was related to more depression, as were high disease activity and poor quality of life [50].

The prevalence of peripheral joint involvement in axSpA was 79.76% in our study, which was quite higher than the 58% found in a Dutch study [52]. The higher the peripheral joint involvement in axSpA, the greater the chance for depression, as observed in our study. The higher rate of peripheral joint involvement in axSpA in Bangladesh deserves further study.

The mean scores of BASDAI, ASDAS-CRP, ASDAS-ESR, ESR, CRP, and ASAS-HI were higher in the depressed group compared to the non-depressed group. A meta-analysis revealed a similar finding [13]. The symptoms as reflected by the BASDAI (pain, stiffness, fatigue) might have a greater impact on the affective state than functional impairments [43]. Of course, the values of ESR or CRP are directly proportional to ASDAS values.

In our study, the quality of life (ASAS-HI) was poor in depressed axSpA patients. A similar observation was reported by others [17,53]. Inflammatory markers (ESR and CRP) were found to be significantly higher in the depressed group in our research, and this finding was consistent with other studies [17,53], although these differences were probably not clinically relevant when considering the large SD.

We found that axSpA with peripheral joint involvement, BASDAI score, and ASAS-HI score were factors related to depression, and the results were compatible with others [17,54].

One may question whether there is an overlap between depression symptoms and those inherent to the disease. This is a question regarding depression questionnaires for any kind of disease, including rheumatic diseases. When depression in AS is measured

with the HADS-D questionnaire, the disease activity as measured with the BASDAI is only weekly related to depression [43], which is in accordance with the findings in our study. In our study, we also applied the PHQ-9 for depression assessment. [55] (data available on request). With that tool, it was possible to divide the cases into mild, moderate, and severe. As the results of both tools were similar, we decided only to use the findings of the WHO-5 questionnaire as a screening tool for depression.

The relationship between depression and cytokines (TNF-α and IL-1β serum levels) in axSpA patients may be complex compared to primary depression. One would expect in depressed people higher cytokine levels. We found a higher IL-1β level in depressed patients with peripheral SPA, although this finding was probably not clinically relevant when considering the large SD. So in practice, in patients with axSpA, cytokine levels are not independent factors regarding depression.

From our observation, we may conclude that depression in axSpA results from an interaction of genetic, environmental, personal, lifestyle, and psychosocial factors with axSpA disease activity.

5. Limitations of This Study

The ASAS-HI scale has not yet been validated for Bangla. In previous studies, differences between countries were found, but these were relatively small and had no major effect on the total score of ASAS HI [50,53]. So we may expect that our findings will not be different after validation.

6. Strength of This Study

To the best of our knowledge, this was the first study determining the association of TNF-α and IL-1β with depression in axSpA patients in Bangladesh and abroad.

7. Conclusions

The levels of serum IL-1β and TNF-α were not significantly related to depression in axSpA patients. Only in depressed patients with peripheral SPA were higher IL-1β levels found, although this finding was probably not clinically relevant when considering the large SD. So in practice, in patients with axSpA, cytokine levels are not independent factors regarding depression.

Peripheral joint involvement in axSpA patients, especially disease activity (CRP, etc.), and reduced health status were associated with depression in axSpA patients.

Associated peripheral joint involvement, BASDAI, and ASAS-HI were independent risk factors for depression in axSpA.

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Abbreviations

ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASAS-HI: Assessment of Spondyloarthritis International Society Health Index; axSpA: Axial Spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; BMI: Body Mass Index; BSMMU: Bangabandhu Sheikh Mujib Medical University; CI: Confidence Interval; CKD: Chronic Kidney Disease; CRP: C-Reactive Protein; DM: Diabetes Mellitus; DMARDs: Disease Modifying Anti-Rheumatic Drugs; ESR: Erythrocyte Sedimentation Rate; HLA-B27: Human Leukocyte Antigen-B27; IBD: Inflammatory Bowel Disease; IBP: Inflammatory Back Pain; IL: Interleukin; IL-β: Interleukin-1 beta; IRB: Institutional Review Board; LBP: Low Back Pain; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MRI: Magnetic Resonance Imaging; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; OR: Odds Ratio; SBMCH: Sher-e-Bangla Medical College Hospital; SD: Standard Deviation; SpA: Spondyloarthritis; TNF: Tumor Necrosis Factor; TNFi: Tumor Necrosis Factor inhibitor; WHO: World Health Organization.

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