# Predictors of not achieving remission or low disease activity in axial spondyloarthritis patients from Middle Eastern countries: A prospective, multicenter, real-world study

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## Abstract

Aim: To identify the predictors of not achieving remission or low disease activity in axial spondyloarthritis patients from some Middle Eastern countries.

Methods: In this multicentre prospective real-world study, adult patients with axial spondyloarthritis diagnosed clinically between January-June 2019 and who met the Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis; were enrolled from the participating centers of four countries namely, Lebanon, Oman, Qatar, and the United Arab Emirates. Patient demographics, disease history, comorbidities, treatment, and compliance data were obtained at baseline.

The primary outcome was to determine the percentage of patients who did not achieve the clinical target of remission or low disease activity (Ankylosing Spondylitis Disease Activity Score–C-reactive protein < 2.1) after a three-month follow-up period. Secondary outcomes were to assess the demographic and clinical characteristics of achievers and non-achievers and to study the predictors of Ankylosing Spondylitis Disease Activity Score–C-reactive protein ≥ 2.1 in different clinical subsets.

Results: Three hundred and nine patients were included (median age 43 years; 53.7% females). At the end of the study, 72.1% of patients reached the clinical target of Ankylosing Spondylitis Disease Activity Score < 2.1. Nonachievers were significantly more likely to have enthesitis, positive human leukocyte antigen-B27 status, psoriasis, peripheral involvement, fibromyalgia, and lower Compliance Questionnaire for Rheumatology (CQR) score. Multiple regression analysis showed that low CQR score, enthesitis, psoriasis, and family history of spondyloarthritis were independent predictors of a higher Ankylosing Spondylitis Disease Activity Score–C-reactive protein ≥ 2.1.

Conclusion: This real-world data showed that low compliance, positive human leukocyte antigen-B27 status, peripheral involvement, and presence of enthesitis, psoriasis, and fibromyalgia were predictors of not achieving remission or low disease activity in axial spondyloarthritis patients.

Keywords: Ankylosing Spondyloarthritis, Middle East, psoriasis, enthesitis, compliance, HLA-B27 antigen, fibromyalgia, peripheral nervous system

## Introduction

Spondyloarthritis (SpA) is a group of interrelated chronic inflammatory diseases with common clinical features, including inflammation of the axial skeleton and peripheral joints, and a close association with the human leukocyte antigen B27 (HLA-B27).[1] The prevalence of spondyloarthritis in the world ranges from 0.2%-2%.[2] In the Middle East, its prevalence has been reported to be as high as 2.2%.[3] The prevalence of HLA-B27 in all SpA patients in the Middle East ranges from 14% to 70%.[4-7]

A growing body of evidence shows that higher disease activity leads to more structural damage in the spine, which correlates with worsening function in the axial form of SpA (axSpA).[8,9]

Over the years, biological therapy has improved work productivity and quality of life in patients with axSpA.[10]Unlike rheumatoid arthritis, the concept of treat-to-target for axSpA is still debated among rheumatologists.[11-13]However, there is a consensus that treatment should be personalized.[14] Several challenges in the Middle East can affect personalized therapeutic decision-making, thus compromising the achievement of remission or at least a low disease activity status.[15,16]

The primary objective of this study was to determine the percentage of axSpA patients who achieved remission and low disease activity (ASDAS-CRP < 2.1) after a three-month follow-up period.

The secondary objectives were to assess the demographic and clinical characteristics of achievers of remission and low disease activity compared to non-achievers and to study the predictors of ASDAS-CRP greater than 2.1 in different clinical subsets.

## Materials and Methods

A multicenter prospective real-world study was conducted in consecutive patients with axSpA consulting rheumatology clinics in Lebanon, Oman, Qatar, and the United Arab Emirates (UAE).

### Patient recruitment

During the Arab League against Rheumatism meeting conducted in Oman (2018), a special interest group met to discuss the current needs of SpA patients in the Middle East. Eight rheumatologists from Lebanon, Oman, Qatar, and UAE expressed interest in participating in a multicentre study to explore the challenges of achieving clinical targets in real-world SpA patients in these countries. The study protocols were reviewed by all investigators and approved by all local institutional review boards and/ or ethics committees.

Consecutive patients who attended the participating centers between January 2019 and June 2019, who were clinically diagnosed as axSpA by the rheumatologist, and who met the Assessment of Spondyloarthritis International Society (ASAS) 2009 classification criteria for axSpA were invited to participate in the study if they were at least 18 years of age and competent to provide informed consent.[17] Patients with peripheral symptoms were also subject to ASAS classification criteria for peripheral SpA to determine patients who had both peripheral and axial SpA; and were included in the study. Patients with only peripheral disease were excluded, patients with axial SpA only or those who had a combination of axial and peripheral features were included. Since the purpose of the study was only to assess real-life data, as per the protocol, the investigators were not required to change their practice or introduce new treatments except for measuring ASDAS in patients with axial disease after 3 months of follow-up.

Data collection

The data and patient consent were collected at the baseline visit of entering the study. All the information including patients' demographics, disease history, comorbidities, and previous use of treatment was noted at baseline and was verified by the patients. The outcome measures of ASDAS and compliance questionnaire were conducted at the 3-month visit. Since there was no introduction of a new treatment to test, given the short period of follow-up, and an aim to represent all the centers, the investigators opted for ASDAS at baseline and 3 months. The investigators relied on the MRI done at the time of the diagnosis to classify patients, it was not done at baseline and during follow-up due to the cost implications.

At the baseline visit, electronic medical records and patient surveys were used to collect the following data:

1. Patient demographics: current age, age at diagnosis, gender, ethnicity, smoking status, marital status, the highest level of education completed, insurance coverage, and access to biologics.
2. Disease history: starting date of persistent symptoms; date on which seen by a rheumatologist for the first time; history of clinical features namely, inflammatory low back pain, arthritis, uveitis, enthesitis at any site (based on clinical evaluation), dactylitis, psoriasis, inflammatory bowel disease, preceding genitourinary infection or diarrhea, nail pitting or onycholysis; laboratory features including C-reactive protein (CRP) and HLA-B27 status; radiographic investigations (radiographic sacroiliitis); family history of SpA; and response to non-steroidal anti-inflammatory drugs (NSAIDs).
3. Comorbidities (as reported by the rheumatologist): diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, degenerative lumbar spine disease,

osteoarthritis, peptic ulcer disease, fibromyalgia, history of tuberculosis, and malignancy.

4. The patients undertook the Compliance Questionnaire for Rheumatology (CQR), which is a self-reported adherence measurement tool created specifically for and validated in rheumatic diseases as against electronic medication event monitors (eMEMs), which is the current gold standard. [18]
5. Treatments: previous and current conventional synthetic disease-modifying drugs (csDMARDs) and biologic DMARDs (bDMARDs) were recorded. Retention rates of treatments received were calculated using the following equation-

$$\frac{\text{Ever received - Discontinued}}{\text{Ever received}} \quad \text{X 100 (converted to a percentage)}$$

This real-world study included axSpA patients regardless of disease duration and treatment status; ever used treatment was recorded for analysis.

Outcome measures

Patients were followed up for three months. The Ankylosing Spondylitis Disease Activity Score (ASDAS) -CRP was assessed at the end of that period. ASDAS-CRP $< 2.1$ was considered as the cut-off point to define achieving clinical target (remission and low disease activity), while ASDAS-CRP $\geq 2.1$ indicated not achieving the target.[19]

The primary outcome was the percentage of patients who achieved remission and low disease activity (ASDAS-CRP $< 2.1$) after a three-month follow-up period. Secondary outcomes were the identification of demographic and clinical characteristics in achievers and non-achievers and the predictors of ASDAS-CRP $\geq 2.1$ in different clinical subsets.

## Statistical analysis

Descriptive statistics, Student's t-test, Mann Whitney U test, and Fisher's exact test were used for statistical analysis as appropriate. Demographic data and disease and treatment characteristics were described as median and the $25^{th}$–$75^{th}$ interquartile range (IQR).

For comparing achievers with non-achievers, we used 2 × 2 tables to calculate the odds ratio (OR) and confidence interval (CI) of different demographic and clinical variables. Chi-square and Fisher's exact test was used to assess the statistical significance of association between rows and columns of categorical variables and t-test was used for continuous variables.

Multiple regression analysis was used to investigate the impact of different factors on ASDAS-CRP ≥ 2.1, used as a continuous variable, in patients with axSpA. Variables included in the different models tested were selected based on their statistical significance in the univariate analysis, and their clinical relevance. Significant variables were finally isolated using stepwise forward selection described as t-value: the coefficient divided by its standard error. All statistical tests were two-sided; a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using Minitab version 18.1 software.

The sample size was based on the estimated total study population size of 1,200. The confidence level of 95%, with a margin of error of 0.05, alpha divided by confidence level was 0.025, and Z-score 1.95. Based on real-world data, ASAS classification criteria (axSpA total) were met in 85.5% of all patients.[18]The sample size required to perform the study was 238 patients.

## Results

Three hundred and nine patients with an established diagnosis of axSpA and who fulfilled the ASAS criteria for axSpA were enrolled from four academic centers and rheumatology clinics

in the Middle East. The median age of patients was 43 years (IQR: 36–51) and 53.7% were females. The median disease duration was six years (IQR: 3–9). Of the 309 patients, 78.9% had radiographic axSpA and 50.2% patients had concomitant peripheral features. Criteria of good response to NSAIDs were used in 21.7% of the patients while classifying them as axial SpA at the time of initial presentation.

At the 3-months visit, 72.1% of patients were within the clinical target of ASDAS < 2.1. Demographic and clinical features are summarized in Table 1.

Comparisons between achievers and non-achievers

Out of 309 patients, 223 patients (72.1%) had an ASDAS < 2.1 at 3 months. On comparing the two groups, patients who did not achieve the clinical target (n = 86) were more likely to have enthesitis, a positive HLA-B27 status, psoriasis, concomitant peripheral involvement, fibromyalgia, and they were less compliant to treatment than those who achieved the clinical target (see Table 2). Interestingly, patients who achieved the clinical target were more likely to stay on csDMARDs and bDMARDs than non-achievers (Table 3). Otherwise, there was no difference between the two groups regarding demographics, clinical features, and treatment used. We compared the percentage of purely axial patients in the achiever (55.7%) and non-achiever group (35.6%). This translated to those patients with axial SpA only having double the chance of achieving desired ASDAS, which was statistically significant (Table 2). On the other hand, patients with axial and peripheral arthritis formed almost two-thirds of the non-achiever group vs 44.3% of the achiever group; the odds ratio of not achieving the desired ASDAS is 2.3 if the patient has axial and peripheral SpA. This significant difference failed to show in the multivariate model including most of the variables included in the study. As 50.4% of patients had radiographic sacroiliitis, the analysis was conducted between patients with radiographic changes and those without radiographic changes. There was no difference in

achieving the target ASDAS on univariate and multivariate analysis. Specific to treatment, the authors compared and concluded that there were no significant differences in treatments received between those who achieved remission/LDA and those who did not.

Predictors of ASDAS-CRP ≥ 2.1

In this prospective study, low CQR score at baseline ($p < 0.0001$), enthesitis ($p = 0.009$), psoriasis ($p = 0.013$), and a family history of SpA ($p = 0.039$) were independent predictors of ASDAS -CRP at three months. Demographic, clinical features, radiographic features, CRP lab values, and coexisting comorbidities were not associated with remission and low disease activity (Table 4).

Discussion

In this real-world, prospective, multicentre study of 309 patients with axSpA from four Middle-Eastern countries, 72.1% of the patients were in remission or had low disease activity as per ASDAS-CRP (< 2.1) after a 3-months follow-up.

The association of higher disease activity with the presence of concomitant peripheral symptoms has been previously reported by de Winter, et al.[20] In his study, patients with both axial and peripheral involvement showed a median ASDAS-CRP level of 3.0 while those with only axial involvement showed a level of 2.6 ($p = 0.014$). Furthermore, the percentage of patients with ASDAS-CRP ≥ 2.1 was higher in those with combined SpA than in those with purely axial SpA. Those patients having both axial as well as peripheral SpA showed a higher prevalence of enthesitis than those with peripheral symptoms alone (62% vs 48%, $p = 0.044$).[20]

The results of the de Winter study reiterate the findings of our study, where 64.4% of patients with concomitant peripheral symptoms were non-achievers (odds ratio = 2.3, $p = 0.007$). Besides, non-achievers were two times more likely to have enthesitis than those who achieved

the clinical target. This was consistent with studies in larger cohorts where enthesitis indices were found to significantly correlate with both axial and peripheral joint involvement and higher disease activity, and with a decline in functional capacity and quality of life.[21,22]

Our study reported a higher prevalence of fibromyalgia among non-achievers compared to achievers of clinical targets (27.9% vs. 11.2%; p = 0.0039). Previous studies have shown higher use of biologics among patients with coexisting fibromyalgia and SpA; a strong association was also seen between multiple switching of biologics and fibromyalgia in patients with SpA.[23]

Treatments such as methotrexate, given to a large percentage of patients, are understandable as nearly half of the patients in our study had concomitant peripheral manifestations. Adherence to therapy is a strong predictor of treatment response.[24] The low CQR scores found among non-achievers in this study can thus act as a predictor of clinical response. In previous studies, non-adherence to biologic therapy was associated with significantly lower response in rheumatic arthritis patients after 6 months of treatment (p = 0.013).[24] Flouri et al. also corroborated the correlation of treatment response with compliance when they showed that first-year treatment response predicts long-term drug persistence in TNFi treated patients with SpA.[25]

In our study, among the non-achievers, reduced treatment retention rates were seen for all bDMARDs. The higher cost may be a likely factor associated with non-adherence to biological therapy.[26] The access to biologic therapies in the Middle East region is variable among countries and depends on the extent of insurance coverage and health provider(s). However, most of the patients in our study had medical insurance coverage, including coverage for bDMARDs. Hence, it is not likely that cost was a reason for non-adherence to treatment in our study. It is known that bDMARDs are potentially immunogenic due to their large molecular size.[27] A secondary failure of biologic agents was attributed to the development of anti-drug antibodies, which in turn was associated with increased risk of

adverse events and poor compliance to therapy.[28] However, we did not report on immunogenicity, given the short duration of follow-up in our study. Other studies in rheumatology patients have however shown that current medication type, treatment beliefs, age, race, comorbidities, smoking, clinical status, high disease activity at the time of diagnosis, decreased quality of life, increased body max index, disease duration, etc. are factors that could predict treatment adherence.[29] A comparison of the response from treatment with anti-TNF inhibitors and IL-17 inhibitors was not made, as the number of patients on IL-17 inhibitors was small to be compared with anti-TNF therapy.
84% of the patients were on anti-TNFs versus 3.9% on IL-17 inhibitors. Hence, there was a risk of Type II error.

Axial SpA shows a very strong genetic association with the major histocompatibility complex (MHC)–encoded class I molecule, HLA–B27. It has been postulated that HLA–B27 contributes to ~40% of the overall risk for axSpA.[30] In our study, only 30% of patients were HLA-B27 positive. Of these, 40% were non-achievers of clinical targets. Our result corroborates with the generally weak association of HLA-B27 seen in Middle East countries (25%-75%) compared with that in Western Europe (>90%).[5,6,31]

Studies have shown that patients with shorter disease duration and better functional status benefit to a greater extent from TNF-blockers.[32] Supporting this, a longer disease duration of 7.5 years was seen among the non-achievers in our study, though this association did not show statistical significance.

Very little data exists regarding axSpA patient populations in the Middle East. Since the study mostly included multinational people of Arabic background, these findings can be applied for the management of SpA in the Middle East area. Compared to other similar studies, the sample size in our study is relatively larger and can be considered as a representative of the axSpA

patient population in this region. In the absence of regional registries, this data assumes significance as it can help understand the region-specific demographic and clinical features of the disease and devise appropriate management strategies.

One of the limitations of the study is that it was conducted at tertiary centers of only 4 countries from the Middle East. More female patients were included in the study. An objective measure of fibromyalgia was not provided in this study. The criterion (a) to differentiate between SpA and fibromyalgia was not included. Additionally, the short follow-up duration of three months may be insufficient to allow proper reporting of extra-musculoskeletal features of SpA that can develop years later (e.g., uveitis).

Conclusion

In our study, 72.1% of axSpA patients achieved the clinical target of remission and low disease activity, as per ASDAS-CRP < 2.1, at 3 months of follow-up. Enthesitis, psoriasis, positive HLA-B27 status, concomitant peripheral involvement, coexisting fibromyalgia, and reduced CQR score were more likely to be associated with non-achievers of clinical targets. Low CQR score, enthesitis, psoriasis, and family history of SpA were independent predictors of a higher ASDAS –CRP (≥ 2.1). The presence of these identified predictors should alert rheumatologists about the need for closer monitoring and intensive follow-up to reach optimal clinical targets.

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**Table 1: Demographic and clinical characteristics of all patients and achievers and non-achievers.**

| Variables | All patients (n=309) | Achievers (n=223) | Non-achievers ( n=86) |
|---|---|---|---|
| Age [Median, (IQR) yrs] | 43, (36-51) | 43, (35-52) | 42, (37-51) |
| Female (%) | 53.7% | 54.2% | 51.9% |
| Disease duration [Median, (IQR) yrs] | 6.0 (3.0-9.0) | 5.0 (2.0-8.0) | 6.0 (2.0-9.0) |
| Patients with medical insurance/ medical coverage (%) | 94.5% | 95.0% | 93.1% |
| Current smoking (%) | 13.9% | 12.1% | 18.6% |
| ASDAS-CRP [Median (IQR)] | 1.9 (1.5-2.7) | 1.5 (1.3-1.6) | 2.9 (2.3-3.4) |
| ASDAS-CRP [Mean] | 2.1 | 1.5 | 2.9 |
| Arthritis (%) | 40.1% | 36.3% | 48.1% |
| Dactylitis (%) | 13.6% | 11.3% | 18.50% |
| Enthesitis (%) | 29.1% | 22.4% | 43.2% |
| Family history of SpA (%) | 18.4% | 14.3% | 25.9% |
| HLA-B27 (%) | 30.8% | 25.6% | 42.5 % |
| Inflammatory bowel disease (%) | 7.1% | 7.3% | 6.20% |
| Inflammatory low back pain (%) | 68.6% | 68.1% | 69.8% |
| Onycholysis (%) | 10.9% | 10.7% | 11.1% |
| Psoriasis (%) | 39.4% | 25.1% | 40.7% |
| Sacroiliitis (Radiographic) (%) Positive findings in X-ray and MRI | 50.2% | 49.8% | 51.9% |

| | | | |
|---|---|---|---|
| Positive findings in MRI not in X-ray | 28.8% | 29.4% | 27.6% |
| Negative findings in X-ray and MRI | 20.7% | 20.8% | 20.5% |
| Uveitis (%) | 6.1% | 4.0% | 11.1% |
| Concomitant peripheral manifestations (%) | 49.3% | 44.3% | 63.9% |
| **Comorbidities** | | | |
| DM (%) | 10% | 9.87% | 11.6% |
| Fibromyalgia (%) | 16% | 11.21% | 27.9% |
| Hypertension (%) | 18% | 16.59% | 20.9% |
| IHD+ stroke (%) | 3% | 3.14% | 3.5% |
| Malignancy (%) | 1% | 1.35% | 1.2% |
| Osteoarthritis (%) | 20% | 20.63% | 16.3% |
| Osteoporosis (%) | 7% | 6.28% | 8.1% |
| Hyperlipidaemia (%) | 8% | 7.17% | 11.6% |

ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-reactive protein; DM: Diabetes mellitus; HLA-B27: Human Leukocyte Antigen B27; IHD: Ischemic heart disease; IQR: Interquartile range; NSAIDS: Non-steroidal anti-inflammatory drugs.

**Table 2: Comparing the non-achievers of clinical targets to achievers.**

| **Variables included in Contingency analysis** | **Achievers 223** | **Non-achievers 86** | **OR** | **CI** | **p-value** |
|---|---|---|---|---|---|
| Enthesitis, N, (%) | 50 (22.4%) | 37 (43.0%) | 2.7 | 1.4 to 5 | 0.0024 |
| HLA-B27, N, (%) | 54 (25.6%) | 34 (42.5%) | 2 | 1.1 to 3.7 | 0.03 |
| Psoriasis, N, (%) | 25.1% | 40.7% | 2.1 | 1.1 to3.8 | 0.02 |
| Concomitant peripheral manifestations N, (%) | 99 (44.4%) | 55(63.9%) | 2.3 | 1.3 to 4.0 | 0.007 |
| Fibromyalgia N, (%) | 25 (11.2%) | 24 (27.9%) | 3.1 | 1.5-6.8 | 0.0039 |
| **Unpaired t-Test** | **Difference between means +SE** | | | **CI** | **p-value** |
| Compliance score | -7.451 ± 1.760 | | | -10.94 to -3.957 | < 0.0001 |

OR: Odds ratio; CI: Confidence interval; HLA: Human leukocyte antigen; SE: Standard error

**Table 3: Comparison of treatments received and retention rates between achievers and non-achievers.**

| Treatment | All patients (n=309) | Achievers (n=223) | | | Non- Achievers (n=86) | | | p value |
|---|---|---|---|---|---|---|---|---|
| | | Ever received | Discontinuation | Retention rate from ever used | Ever received | Discontinuation | Retention rate from ever used | |
| Methotrexate | 42.4% | 43.0% | 9.4% | 78.1% | 40.7% | 26.7% | 34.3% | 0.0001 |
| Salazopyrine | 35.6% | 35.9% | 11.2% | 68.8% | 34.9% | 15.1% | 56.7% | N.S. |
| Leflunomide | 6.8% | 6.3% | 4.0% | 35.7% | 8.1% | 5.8% | 28.6% | N.S. |
| Etanercept | 22.3% | 20.2% | 8.1% | 60.0% | 27.9% | 16.3% | 41.7% | 0.01 |
| Adalimumab | 33.3% | 31.4% | 7.6% | 75.6% | 38.4% | 19.8% | 48.5% | 0.0001 |
| Infliximab | 12.6% | 12.1% | 4.9% | 59.3% | 14.0% | 8.1% | 41.7% | 0.02 |
| Golimumab | 8.4% | 4.50% | 1.3% | 70.0% | 18.6% | 7.0% | 62.5% | N.S. |
| Secukinumab | 3.9% | 2.2% | 0% | 100.00% | 8.1% | 2.3% | 71.4% | 0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Certolizumab pegol | 7.4% | 4.9% | 1.80% | 63.6% | 14.0% | 3.5% | 75.0% | N.S. |

**Table 4: Predictors of ASDAS ≥ 2.1 in axSpA patients from the Middle East.**

| **Variables** | **Coef** | **SE Coef** | **95% CI** | **p-value** |
|---|---|---|---|---|
| Compliance score | -0.01890 | 0.00434 | (-0.02746, -0.01035) | 0.000 |
| Enthesitis | 0.308 | 0.117 | (0.077, 0.539) | 0.009 |
| Psoriasis | 0.276 | 0.111 | (0.058, 0.493) | 0.013 |
| Family history of SpA | 0.257 | 0.124 | (0.013, 0.501) | 0.039 |

SE Coef: Standard error of the coefficient; CI: Confidence interval