Towards an Earlier Diagnosis of Axial Spondylarthritis: Performance of clinical variables in a spondylitis screening clinic

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Background

- There is a window of opportunity in the treatment of axial spondylarthritis (AxSpA). The diagnosis is often delayed due to a lack of pathognomonic clinical features and biomarkers for this disease.

Objectives

- A prospective study was performed on patients presenting with undifferentiated back pain to identify factors aiding in the diagnosis of AxSpA.

Methods

- Adults with low back pain (LBP) attending the Inter-professional Spine Assessment and Education Clinic (ISAEC)[1] were referred to a spondylitis screening clinic (SSC) if they had LBP for more than 3 months and their age-of-onset was < 50. In the SSC, assessment was done by a physiotherapist and rheumatologists, both with axSpA expertise. Final diagnosis was made by the rheumatologist following clinical examination and interpretation.
- MRI was done only if deemed clinically indicated by the rheumatologist.
- We first validated an existing diagnostic approach for AxSpA by Poddubnyy et al. (2021) that used probability estimations based on likelihood ratios (LR) and pre-test disease probability.
- Next, we used the same methodology, but including only variables that were significant on univariable regression in our data, in addition to variables deemed clinically important (sex and age).
- We used the machine learning model Elastic-net regression, a regularization technique. The discrimination ability of each model was assessed by comparing the area under (ROC) curves and appropriate internal cross validation was conducted to ensure robustness of the models.

Results

Table 1: Descriptive Statistics

Co-Variate	Total (N = 359)	MBP (N = 298)	AxSpA (N = 61)	P
Age (Years, SD)	37.3 (10.1)	37.7 (10.1)	35.4 (9.8)	0.10
Gender (Male, %)	164 (46)	129 (43)	35 (57)	0.06
Back Pain at Rest (SD)	4.8 (2.5)	4.7 (2.4)	5.2 (2.7)	0.26
Back Pain with Activity (SD)	6.2 (2.5)	6.1 (2.5)	6.3 (2.6)	0.78
ODI Score (0-100, SD)	31.4 (16.8)	30.7 (16.4)	34.9 (18.7)	0.15
EQ-5D Health Utility Index (0-1, SD)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.18
Self-Efficacy Score (SD)	6.7 (2.0)	6.7 (2.0)	6.4 (2.1)	0.32
Back Pain Duration (Years, SD)	8.0 (8.2)	7.9 (8.4)	8.2 (7.7)	0.62
Morning Stiffness > 30 minutes (%)	261 (74)	214 (73)	47 (78)	0.42
Presence of Nocturnal Symptoms (%)	187 (52)	156 (53)	31 (52)	1.00
Better with Activity (%)	207 (58)	173 (58)	34 (58)	1.00
Improves with Rest (%)	153 (43)	128 (43)	25 (42)	1.00
Alternating Buttock Pain (%)	46 (13)	33 (11)	13 (22)	0.03
At Least One Feature of IBP	337 (94)	282 (95)	55 (90)	0.30
At Least Three Features of IBP	176 (49)	141 (47)	35 (57)	0.20
Number of IBP features (SD)	3.3 (1.1)	3.3 (1.1)	3.4 (1.1)	0.32
NSAID Responsiveness (SD)	2.1 (1.4)	2.0 (1.4)	2.5 (1.4)	0.01
HLA-B27 (Positive, %)	47 (13)	25 (8)	22 (36)	<0.001
CRP > 10 (%)	13 (5)	7 (3)	6 (14)	0.008
ESR (SD)	7.8 (8.7)	7.5 (8.8)	9.1 (8.4)	0.15
# Of Extra-Articular Features (0-5, SD)	0.1 (0.4)	0.1 (0.3)	0.2 (0.5)	0.14
Enthesitis (At Least One, %)	136 (38)	103 (35)	33 (54)	0.007
Dactylitis (At Least One, %)	91 (25)	66 (22)	25 (41)	0.004
Family History of AS (%)	7 (2)	6 (2)	1 (2)	1.00
Peripheral Joint Involvement (Any, %)	86 (24)	74 (25)	12 (20)	0.41
Modified New York Criteria Positive	37 (10)	7 (2)	30 (49)	<0.001
Positive MRI (N, % of MRIs performed)	41 (28)	1 (1)	40 (93)	<0.001

ODI = Oswestry Disability Index, EQ-5D = EuroQol Five-Dimensions, IBP = Inflammatory Back Pain, NSAID = Non-Steroidal Anti-Inflammatory Drug, CRP = C-Reactive Protein, ESR = Erythrocyte Sedimentation Rate.

Results

Table 2: The ranking of AxSpA features in our data using the LR method (Poddubnyy et al. 2021)

Variable	LR (+)	LR (-)	Pre-Test Prob.	Post-Test Prob. TP	Post-Test Prob. TN
Modified New York Criteria	11.55	0.52	0.2	0.74	0.12
CRP ≥ 10	4.98	0.88	0.2	0.55	0.18
HLA-B27 Positivity	3.70	0.74	0.2	0.48	0.16
Good Response to NSAID	2.11	0.72	0.2	0.35	0.15
At Least 3 Features of IBP	2.05	0.19	0.2	0.34	0.05
Sex (Male)	1.64	0.66	0.2	0.29	0.14
Dactylitis	1.59	0.81	0.2	0.28	0.17
Enthesitis	1.54	0.71	0.2	0.28	0.15
Young Age (<37 years)	1.01	0.98	0.2	0.20	0.20

Table 3: Ranking of AxSpA features by importance using Elastic-net regression

Variable	OR
Modified New York Criteria	2.86
At Least 3 Features of IBP	1.85
HLA-B27 Positivity	1.72
CRP ≥ 10	1.60
Dactylitis	1.38
Good Response to NSAIDs	1.31
Sex (male)	1.33
Enthesitis	1.23
Young Age (Age<37)	0.99

- Out of the 359 patients enrolled in the study, approximately 17% had a diagnosis of AxSpA.
- Many of the variables of importance in Poddubnyy et. al's 2021 study were also found to be of importance in our dataset including having definite radiographic sacroillitis defined as bilateral grade 2 or unilateral grade 3 according to the grading system of the Modified New York criteria, CRP Elevation, HLA-B27 positivity, as well as at least 3 features of IBP.
- When evaluating the development of Likelihood Ratios (LRs) from clinically significant predictive variables (Table 2), the cross-validation Area Under the Curve (AUC) was found to be **0.81** with a 95% Confidence Interval (CI) of (0.58, 1). From the elastic net regression model, AUC was found to be **0.82** with a 95% CI (0.61,1) for the same predictive variables used in the LR method.

Conclusions

The proportion of AxSpA among patients referred through the ISAEC program to SSC was higher than the 5% prevalence of AxSpA noted within the literature. Key risk factors identified in another study were validated. A better performing AxSpA diagnostic model with with the relative contributions of the included variables are presented here through our cross-validation study. By further refining these predictive models, we can strive to achieve an earlier diagnosis of this condition.

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