THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 9

RESEARCH ARTICLE

Factors associated with multiple biologic switches in Axial Spondyloarthritis: Exploring real world clinical data with clustering analysis

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OPEN ACCESS

PUBLISHED
30 September 2024

CITATION
Dua, D., Gullick, N., et al., 2024. Factors associated with multiple biologic switches in Axial Spondyloarthritis: Exploring real world clinical data with clustering analysis. Medical Research Archives, [online] 12(9). https://doi.org/10.18103/mra.v12i9.5848

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DOI
https://doi.org/10.18103/mra.v12i9.5848

ISSN
2375-1924

ABSTRACT

Introduction: Axial Spondyloarthritis is a complex and heterogenous disorder. The disease varies significantly leading to a diverse spectrum of management choices. We analysed retrospective clinical data from our centre to identify factors associated with multiple biologic switches. We used clustering analysis, an unsupervised machine learning algorithm, and multivariate logistic regression.

Aim: To identify factors associated with a higher frequency of biologic switches in axial spondyloarthropathy patients in a real-world clinical setting.

Materials and Methods: Data were collected retrospectively from the consultations of 166 patients receiving biologic treatment for axial spondyloarthropathy at our centre from 2003 until 2021. Feature selection included: demographics; body mass index; clinical phenotype (axial involvement; peripheral arthritis; enthesitis; uveitis; psoriasis; inflammatory bowel disease); HLA-B27 positivity; radiographic disease; chronic widespread pain diagnosis; disease activity measures (baseline and aggregate scores over disease course) – Bath Ankylosing Spondylitis Disease Activity Index; Spinal pain Visual Analogue Score; Bath Ankylosing Spondylitis Functional Index; C-reactive protein; time to start biologic from diagnosis; number of biologics and mode of action. Clustering analysis included two additional variables: – response to Tumour Necrosis Factor inhibitors and Interleukin-17 inhibitors. Patients were defined as high biologic switchers if they received three or more biologics (not including non-medical switches to biosimilar agents). Multi-variate logistic regression was performed using *MNLogit* algorithm and clustering analysis using the *k-means* algorithm (Anaconda Distribution 2.7).

Results: Clustering partitioned our dataset into three clusters: Low Disease Burden (LDB), High Disease Burden 1(HDB1) and High Disease Burden 2(HDB2). The LDB cluster showed good response to treatment, lower disease activity scores and fewer treatment switches. HDB clusters had higher disease activity scores; however, the HDB1 patients had significantly fewer biologic switches. Common features of the HDB1 cluster were female sex, HLA-B27 negativity, less radiographic disease, and more chronic widespread pain diagnosis. Multivariate logistic regression showed that HLA-B27 positivity and higher disease activity scores were positively associated with more biologic switches, whereas time to start biologic and a diagnosis of chronic widespread pain were negatively associated.

Conclusion: HLA-B27 positivity, male sex, higher radiographic burden, higher disease activity scores and early biologic requirement were associated with more biologic switches. Females with axial spondyloarthropathy, HLA-B27 negativity and lower radiographic disease burden had significantly fewer biologic switches despite higher disease activity scores and were more likely to have accompanying chronic widespread pain. Despite advances in treatment, patients with high symptom burden pose a challenge in clinical practice. Consideration should be given to objective and holistic assessment of symptoms and treating other associated conditions, as necessary.

Abbreviations:

AI: Artificial Intelligence
ASDAS: Ankylosing Spondylitis Disease Activity Score
axSpA: Axial Spondyloarthritis
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Function Index
bDMARD: Biologic Disease Modifying Anti Rheumatic Drugs
BMI: Body Mass Index
BMP: Bone Morphogenetic Protein
CRP: C-Reactive Protein
CTLA4: Cytotoxic T-Lymphocyte Antigen 4
DMARD: Disease Modifying Anti Rheumatic Drug
IL12: Interleukin 12
IL12i: Interleukin 12 Inhibitor
IL17: Interleukin 17
IL17i: Interleukin 17 Inhibitor
IL23: Interleukin 23
IL23i: Interleukin 23 Inhibitor
nr-axSpA: Non-radiographic Axial Spondyloarthritis
PTPN22: Protein Tyrosine Phosphate Nonreceptor 22
r-axSpA: Radiographic Axial Spondyloarthritis
TNF: Tumour Necrosis Factor
TNFi: Tumour Necrosis Factor Inhibitor
tsDMARD: Targeted Synthetic Disease Modifying Anti Rheumatic Drugs
VAS: Visual Analogue Score
Wnt: Wingless Transmitter

Introduction

Axial spondylarthritis (axSpA) is the most common arthritis affecting the axial skeleton, with an estimated prevalence of 1.4[1]. It is a complex and heterogenous disorder, which exhibits considerable variability in clinical, immunological, molecular, and radiological phenotypes. The clinical spectrum extends beyond the axial skeleton; there are numerous extra-musculoskeletal manifestations such as uveitis, dactylitis, enthesitis, and peripheral arthritis, alongside comorbidities like psoriasis and inflammatory bowel disease (IBD)[2-5]. axSpA patients frequently experience fatigue, and there is a notable association with fibromyalgia[6-8]. AxSpA can be radiographic (r-axSpA, previously referred to as Ankylosing Spondylitis) or non-radiographic (nr-axSpA), depending on the presence or absence of structural damage on x-rays of the sacroiliac joints[1].

Our understanding of the disease process is constantly evolving. Previously, significant male predominance was described with a male to female ratio of 9:1. Recent studies have now found this to be 2-3:1 for radiographic disease and 1:1 for non-radiographic disease, suggesting an increased awareness of the disease process in female patients and better access to effective treatment[9-11]. A similar shift is occurring in our understanding of the genetic risk factors for disease development. While HLA-B27 continues to be the best known and studied genetic haplotype for this condition, we now know that it accounts for only ≈25% of the heritable component of this illness[12]. Proteins like protein tyrosine nonreceptor 22 (PTNP 22) and cytotoxic T lymphocyte antigen 4(CTLA4) are also implicated in the molecular pathogenesis[13]. Perhaps the most notable shift in our understanding of the disease has come with the recognition of immunological complexity; several cytokine and bone pathways have been identified as drivers of this disease process including tumour necrosis factor (TNF), interleukin 17 (IL17), interleukin12(IL12)/ interleukin 23(IL23), Janus associated kinases (JAK), bone morphogenetic protein (BMP), Wnt signalling pathway. The recognition of these pathways has generated multiple therapeutic targets and revolutionised the treatment of axSpA. The availability of multiple therapies targeting TNFα, IL-17A or F, or JAK isoforms have made the goals of disease control and remission achievable[14-18]. These drugs have the potential to lead us into an era of personalised medicine for management of axSpA.

However, there continue to be significant gaps in knowledge which hinder achievement of excellent outcomes for all patients. Currently, there are no reliable variables which can predict response to specific treatment or be used for monitoring response to therapy[19]. It is recommended that therapeutic decision-making, including initiation of biologic disease modifying anti-rheumatic drugs (bDMARDs)/ targeted synthetic DMARDs (tsDMARDs) be undertaken by a rheumatologist with shared decision making with an individual[16-18]. Assessing disease activity is a complex process which relies on clinical assessment in conjunction with validated composite disease activity measures, serum acute phase reactants, imaging, and patient reported outcome measures. Of these, composite disease activity measures such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Ankylosing Disease Activity Score (ASDAS), are best studied and most reliable[20,21]. However, these measures may not always reflect active inflammation due to the subjective nature of parts of the assessments.

With time our understanding of what constitutes 'disease activity' has also evolved; a more comprehensive approach to patient management includes assessment of domains which impact a patient such as pain, fatigue, function, sleep, social health, and ability to work[20,22-25]. These are commonly collected in the clinical trial setting, and not often assessed in routine clinical practice. These changing measures reflect the expansion in our understanding of both the disease process and its impact on patients. The goal posts of axSpA therapy are constantly shifting to make sure that control is achieved in all these complex, and at times, highly subjective domains.

It is not possible for this degree of heterogeneity and complexity to be adequately captured by intervention trials with their rigid inclusion and exclusion criteria. Studying real-world clinical data can help gain a broader and more comprehensive view of the disease process and impact[26]. The aim of our study was to try to identify factors associated with multiple biologic switches using a real-world clinical dataset of axSpA patients. Identification of these factors can potentially improve treatment selection for individual patients and help understand barriers which prevent achievement of clinical remission or low disease activity in a real-world setting. We used two different analytic techniques – Clustering analysis, a statistical method capable of handling heterogenous, complex data including mixed data types, and multivariate logistic regression which looks at the

association of multiple variables with a predetermined binary outcome. Clustering analysis segregates data into groups based on similarity; it does not require a predefined outcome variable and can therefore discover hidden structures within a given dataset[27]. This allows discovery of previously unrecognised trends and can lead to generation of new hypotheses, which are rooted in statistical fact. Multivariate logistic regression requires a predefined binary outcome variable. While this has the drawback of imposing an arbitrary structure onto a dataset, it is useful for assessing a pre-defined hypothesis and delineating the strength of the association a given variable has with the outcome measure. Using both techniques on a given dataset can potentially allow for a more thorough analysis and generate deeper insight into complex datasets.

Methods & Results:

STUDY POPULATION

Data were collected retrospectively from the clinical consultations of 166 patients receiving targeted therapies for axSpA at our centre from 2003 until 2021. Feature selection included demographics, body mass index(BMI), clinical phenotype (axial involvement; peripheral arthritis; enthesitis; uveitis; psoriasis; inflammatory bowel disease, presence of HLA-B27, presence of radiographic disease; chronic widespread pain diagnosis; disease activity measures (both baseline as well as aggregate scores over disease course) – Bath Ankylosing Disease Activity Index(BASDAI); Spinal pain Visual Analogue Scores(VAS); Bath Ankylosing Spondylitis Functional Index(BASFI); C-Reactive Protein(CRP); time to start biologic from diagnosis; number of biologics and mode of action[28-30]. Our outcome variable was 'received multiple biologic switches' defined as those who received ≥ 3 biologics (with different modes of action). Given the variability of follow-up times in our real-world setting, the aggregate scores were averaged (sum of disease activity scores collected biannually divided by number of years of follow-up) to ensure standardisation. Clustering analysis included two additional variables: response to first TNFi and first IL17i. This was assigned a numerical code: 1- Good, sustained response, 1- Primary non-response, and 2- secondary non-response. These two variables were included in clustering to better understand the trends in response to individual biologics in our cohort. They were excluded from multivariate logistic regression as missing data could not be imputed for.

DATA ANALYSIS

Two distinct statistical techniques were applied to the same dataset: Clustering Analysis and Multivariate Logistic Regression. Clustering analysis using the *k-means* algorithm and multi-variate logistic regression was performed using *MNLogit* algorithm (Anaconda Distribution 2.7)[31]. Clustering analysis was chosen because it is an unsupervised learning method that does not require predefined outcome sets or labels. This approach is ideal for exploring the natural structure and patterns within the data, allowing us to group similar observations based solely on their characteristics.

To answer the question posed by our study, i.e. identifying factors associated with multiple biologic switches we chose the technique of multivariate logistic regression. Our outcome variable is binary categorical – received multiple biologic switches/ did not receive multiple biologic switches; and multivariate logistic regression is specifically designed to model the relationship between multiple independent variables and a binary outcome. This method allows us to estimate the probability of a particular outcome (in this case received multiple switches) based on a combination of predictors, making it ideal for scenarios where the dependent variable is categorical. It is also well suited for handling multiple input variables as it reduces redundancy by simultaneously considering multiple variables, naturally downweighing those that are redundant. It manages collinearity through model adjustments, such as regularization or variable selection, ensuring that the final model is stable, interpretable, and free from the distortions caused by codependent variables.

DATA PROCESSING AND ARCHITECTURE FOR CLUSTERING ANALYSIS VS. MULTIVARIATE LOGISTIC REGRESSION

The data architecture required for clustering analysis and multivariate logistic regression differs significantly due to the distinct nature and objectives of these techniques. Below is a breakdown of the key differences in our dataset depending on the analytic technique being applied.

CLUSTERING ANALYSIS:

Data Preparation:

- **Feature Selection:** All of the features outlined above were stored in numeric format – some like age, CRP, BASDAI, number of therapies were by nature numeric; others like radiographic disease, HLA-B27 positivity, chronic widespread pain were assigned a numeric value (0=absent, 1=present for binary possibilities); gradations from 0-4 were used for radiographic severity assessment in accordance with the New York criteria for sacroiliitis grading.
- **Normalization/Standardization:** All features were scaled to ensure that they contribute equally to the distance metrics used in clustering (K-means relies on Euclidean distance).
- **Managing Missing Data:** Missing values were imputed by substituting mean or median for the data group.

Processing: K-means algorithm was applied to the data set using Anaconda Python 3.7 distribution. This algorithm calculates pairwise distance between data points, assigns them to a cluster and iteratively repeats this process till convergence is achieved. The number of clusters was determined using elbow method, for our study this was 3.

Multivariate Logistic Regression:

Data Preparation:

- **Feature Selection:** Our feature set was divided into 'predictor variables' and 'outcome variable.' For this study we set the outcome variable as those with/ without 'multiple biologic switches' - defined as requirement of ≥3 different biologics/tsDMARDs and/ or targeting ≥ 2 biologic pathways.
- **Managing Missing Data:** Missing values were imputed using mean or median.

Processing: A model capable of accurately classifying patients into the binary outcome category (multiple biologic switches or not) using the predictor variables was built using the maximum likelihood estimation algorithm in Anaconda Python 3.7 package. In this model, the relationship of each variable with the outcome variable is assessed for significance using p-value (the probability computed assuming the null hypothesis is true). A p -value ≤ 0.05 was considered statistically significant.

Results:

DEMOGRAPHICS

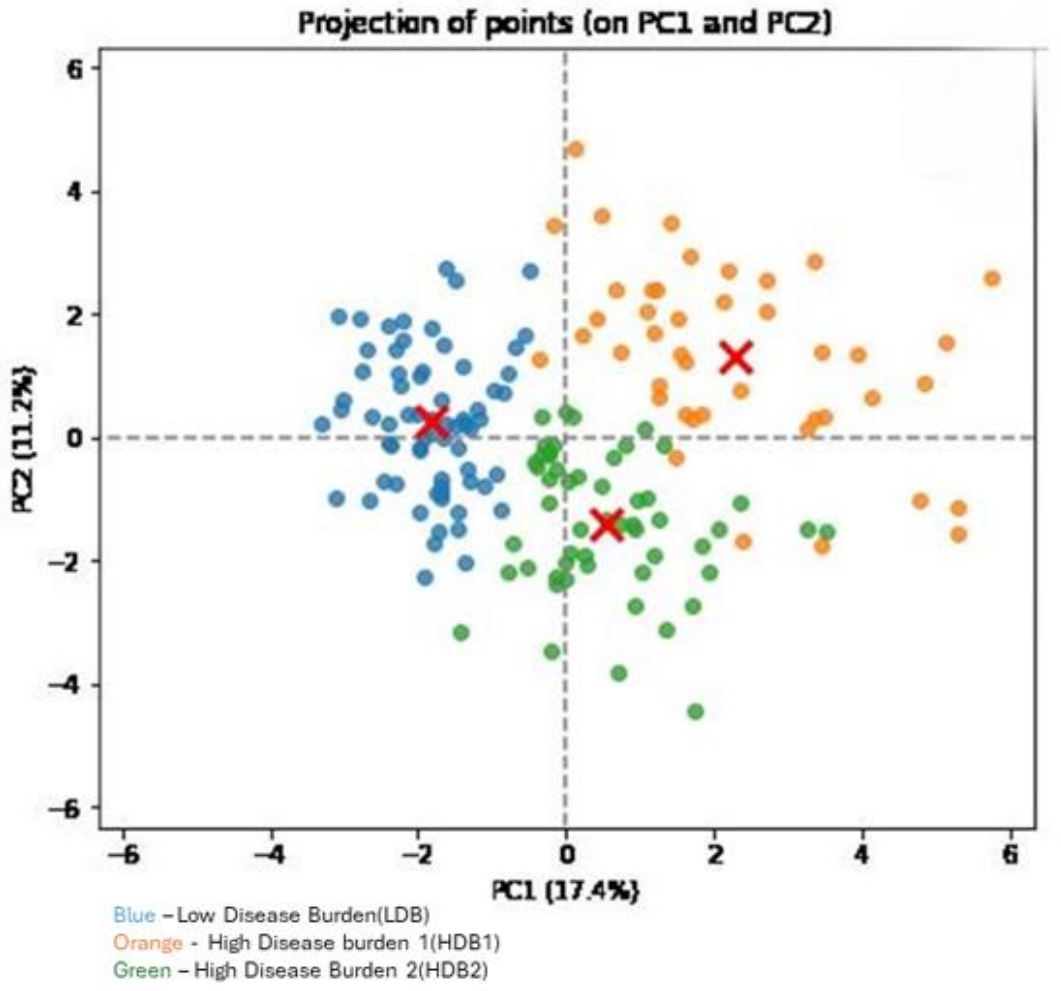
Of the 166 patients included in our study, sixty-two met the definition for multiple biologic use. There were 117 men and 49 women. The average age of patients who received multiple biologic switches was 46.1 years and those who did not was 48.9 years. The average age at diagnosis of patients with multiple biologic switches was 32.7 years and those without was 34.5 years. The mean BMI of patients with multiple biologic switches was 28.6 and those without was 27.8.

CLUSTERING ANALYSIS:

K-means clustering analysis identified three clusters (Figure 1):

1. **Cluster 1 (LDB - Low Disease Burden; Blue cluster):** Male, high HLA-B27 positivity, lowest burden of CWP, lowest baseline and aggregate BASDAI and pain VAS scores. This cluster had the best response rates to TNFi and IL-17i, and therefore did not meet the multiple biologic use criteria defined for this study.
2. **Cluster 2 (HDB1 - High Disease Burden with Chronic Widespread Pain; Orange cluster):** Female, highest burden of CWP, high baseline and aggregate BASDAI and pain VAS scores, lowest radiographic burden. This cluster had the highest rate of TNFi and IL-17i failures but tended to not meet the criteria for multiple biologic switches.
3. **Cluster 3 (HDB2 - High Disease Burden without Chronic Widespread Pain; Green cluster):** Male, high HLA-B27 positivity and radiographic burden, similar high baseline and aggregate BASDAI and pain VAS scores as HDB1. This cluster also had high treatment failure rates and has cycled through multiple targeted therapies.

Figure 1: K-means Clustering of 166 axSpA patients.



Multivariate analysis:

Multivariate analysis identified significant factors associated with multiple biologic switches (Table1): HLA-B27 positivity and high aggregate BASDAI scores were positively associated with multiple biologic switches; receiving targeted therapies later in the disease course and presence of chronic widespread pain were negatively associated with multiple treatment switches. The most significant predictor was the time from diagnosis to the start of targeted therapy (p=0.003).

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Table 1: Patient and disease characteristics according to presence/ absence of multiple biologic switches.

	Multiple biologic switches	Others	P-value
HLA-B27 positivity %	41 (66)	51 (49)	0.038
Time to start biologic from diagnosis, mean (SD), years	4.7 (6.1)	7.3 (8.1)	0.003
Uveitis %	12 (19)	27 (26)	0.443
Psoriasis %	9 (14)	15 (14)	0.757
Peripheral joint involvement %	18 (29)	34 (33)	0.631
IBD %	6 (10)	8 (8)	0.617
Nr-axSpA %	7 (11)	17 (16)	0.098
Concomitant CWP syndrome diagnosis %	7 (11)	20 (19)	0.015
Baseline BASDAI, median (IQR)	7 (1.8)	6.7 (2.2)	0.191
Baseline pain VAS, median (IQR)	7.3 (1)	7.3 (2)	0.412
Baseline CRP, mg/L, median (IQR)	22.5 (46.5)	22 (28.5)	1.000
Aggregate BASDAI, median (IQR)	5 (1.8)	3.2 (2.7)	0.011
Aggregate pain VAS, median (IQR)	5 (2.4)	3.5 (3)	0.165
Aggregate BASFI, median (IQR)	4.3 (3.6)	3.4 (3.6)	0.098

Discussion:

In this real-world, retrospective study we analysed clinical data of 161 patients to identify factors associated with multiple biologic switches. Our results showed that male sex, HLA-B27 positivity, higher radiographic burden, higher baseline and aggregate BASDAI scores, and early biologic requirement were associated with multiple biologic switches. Female sex, less HLA-B27 positivity, lower baseline and aggregate BASDAI scores, more chronic widespread pain, and less radiographic disease were negatively associated with high biologic use. Clustering analysis uncovered an important subset in our patient population. The HDB1 cluster, which had more women, more chronic pain, less radiographic disease, and less HLA-B27 positivity, did not fulfil the high biologic use criteria despite having high aggregate BASDAI and pain VAS scores. In contrast, the HDB2 cluster with more men, higher HLA-B27 positivity, and more radiographic disease did fulfil the high biologic use criteria. The aggregate pain and disease activity scores in this cluster were like those in HDB1.

Identification of variables that can predict biologic response in axSpA is an area of substantial interest[32-35]. At an individual level, it can impact a patient's day-to-day symptoms and risk of flares, which in turn affect patient's disease activity and quality of life scores. At a broader level, it can direct appropriate resource allocation by identifying areas of need. Many studies are now opting to use machine learning algorithms because of their ability to manage complex data and outperform conventional statistical models. We did not find a study which specifically looked at multiple biologic use in axSpA in our literature review, although there are numerous studies assessing predictors for TNFi response in axSpA[32,34]. In one of these studies, a machine learning model was developed to predict response to first TNFi use in axSpA; and it found that higher disease activity scores, higher erythrocyte sedimentation rate (ESR) and CRP, and younger age all predict response[36]. This is different from our results, where longer times for biologic initiation were associated with better response and fewer switches. This contradiction highlights the heterogenous nature of real-world clinical data; there could be local differences in study population and treatment practices which account for this difference and which would be impossible to capture in a pseudo-homogenised setting of trial datasets. For context, the patients in our study who had a later biologic initiation tended to have a milder disease with less treatment requirement.

Several studies have shown that female sex is associated with decreased responsiveness to TNFi[9,10,32,37]. A recent one found that female sex, delayed treatment initiation, and presence of comorbidities were associated with an unfavourable response to TNFi[9]. The researchers went on to use AI-based data analytic techniques which demonstrated a potential relationship between female sex and the age at diagnosis at the beginning of the treatment with an unfavourable response to TNFi. According to their research, female sex was frequently associated with later age at diagnosis, and it was the combination of these two factors rather than gender per se which was significantly associated with unfavourable response rates. Although the evidence was not conclusive, it did suggest that delayed diagnosis in women impacts their treatment response rates. Other studies, looking into sex difference in axSpA, found that women have more pain, less radiographic disease, and a higher incidence of peripheral arthritis than men[10,11,38]. An overarching theme which emerged from our literature review is that axial spondyloarthropathy behaves differently in men and women. Additionally, diagnostic delays and delays in therapy initiation among women are a common occurrence; and all this potentially contributes to the reduced responsiveness to TNF inhibition observed in women.

The results from our clustering analysis spotlight a similar trend; women with high pain, high disease activity burden, and less radiographic disease, have poorer treatment responses to both TNFi and IL17i. They are also more likely to have a concomitant diagnosis of chronic widespread pain, and overall lower use of targeted therapies compared to men with similar pain and disease activity scores. The multivariate logistic regression results complimented those of clustering analysis, with HLA-B27 positivity and high aggregate BASDAI achieving significant positive association with multiple biologic switches; and chronic widespread pain and time to start

biologic from diagnosis achieving significant negative association with it.

Although the evidence presented in our study is far from conclusive, it does suggest that women with axSpA and chronic widespread pain make up an area of unmet need that would benefit from more dedicated research to better understand their specific disease phenotypes rather than extrapolating knowledge from the traditional, male-predominant study of axSpA onto them. There are well-documented differences in the immunologic and genetic factors involved in the axSpA disease process affecting men and women[39,40]. There is also hormonal influence on immune system function in women, which can further alter disease expression. Additionally, there can be differences in healthcare provider's perception of axSpA in men and women, which leads to more diagnostic delay and often later initiation of biologic treatment in women[10]. It is possible that these differences contribute to the poorer treatment responses experienced by women.

It is also important to recognise the role holistic patient management can play in bridging healthcare gaps such as the one identified by our study. Exercise, for instance, has been found to modulate the inflammatory cytokine profile in axSpA and is now recognised as a potential disease modifier[41]. An area of future research would be to study holistic axSpA management; incorporating exercise, physiotherapy, and pain management in addition to pharmaceutical disease modifying therapy, in specific patient groups to see if they can help meet the disease control goals not fully realised with biologic therapy.

An intriguing finding of our study was the association of HLA-B27 positivity with multiple biologic switches. Previous studies have found HLA-B27 positivity to be associated with good response to TNFi which, one would presume, lead to fewer need for switches[33,34]. Our results suggest that HLA-B27 positive patients may be more likely to be considered to have active disease and are therefore offered more biologic switches.

The strengths of our study include the use of real-world clinical data which is essential for gaining a broader perspective of the disease process. Additionally, we used clustering analysis, a machine learning algorithm which is well suited to delineating the natural, hidden structure of a dataset. It outlines trends which exist, bringing them into sharper focus and mitigates the bias which comes with the use of predefined outcome variables.

The limitations are the smaller patient population, and that data were collected from a single centre. Therefore, it may not be representative of the full spectrum of disease and clinical behaviour at a broader level. There was considerable heterogeneity in terms of disease duration of our cohort which can influence the results, although we endeavoured to standardise all the information to mitigate this effect. There is also potential for bias of individual clinicians to influence our results.

Conclusion

In conclusion, our study highlights the complexity of axSpA as a disease process, especially in context of biologic treatment responses. The use of both clustering analysis and multivariate logistic regression generated different, though complimentary insights, spotlighting the importance of using novel statistical approaches to broaden the scope of knowledge a dataset has to offer. In this study, the integration of these analytic techniques not only helped identify factors associated with multiple biologic switches but also uncovered distinct patient subsets in our cohort who stand to benefit from a more tailored therapeutic approach. Of note were the differences in treatment responsiveness observed between men and women, a trend corroborated by other studies. There is sufficient evidence to suggest that the evolution of axSpA as a disease in women is innately different when compared with men, this is further complicated by the lack of evidence-based knowledge about the disease process and its management in women. A key takeaway from our analysis is how data bias disproportionately affects certain patient populations. Women with concomitant chronic widespread pain diagnosis are not well represented in randomised controlled trials; and our study demonstrates how this translates into a significant lack of evidence-based treatment options for this group. This subgroup is burdened with higher disease activity scores *and* have fewer treatment options offered to them. While our findings are limited by the study's retrospective design and single-centre data, they provide valuable insights that warrant further investigation. Future research should focus on understanding the specific disease phenotypes in women with axSpA, or those with chronic widespread pain, exploring the underlying mechanisms driving the observed differences in treatment outcomes, with the goal of improving personalized care in this patient population.

Conflict of interest statement:

The authors have no conflicts of interest to declare.

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References

1. Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. N Engl J Med. 2016 Jun 30;374(26):2563–74.
2. Bengtsson K, Forsblad-d'Elia H, Deminger A, Klingberg E, Dehlin M, Exarchou S, et al. Incidence of extra-articular manifestations in ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis: results from a national register-based cohort study. Rheumatol Oxf Engl. 2021 Jun 18;60(6):2725–34.
3. El Maghraoui A. Extra-articular manifestations of ankylosing spondylitis: prevalence, characteristics and therapeutic implications. Eur J Intern Med. 2011 Dec;22(6):554–60.
4. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis. 2015 Jan;74(1):65–73.
5. Zhao SS, Radner H, Siebert S, Duffield SJ, Thong D, Hughes DM, et al. Comorbidity burden in axial spondyloarthritis: a cluster analysis. Rheumatol Oxf Engl. 2019 Oct 1;58(10):1746–54.
6. Son SM, Kim DS, Lee JS. Fibromyalgia in Axial Spondyloarthritis: A Meta-analysis. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2022 Jan 1;28(1):e222–7.
7. Macfarlane GJ, Pathan E, Siebert S, Packham J, Gaffney K, Choy E, et al. AxSpA patients who also meet criteria for fibromyalgia: identifying distinct patient clusters using data from a UK national register (BSRBR-AS). BMC Rheumatol. 2019;3:19.
8. Rencber N, Saglam G, Huner B, Kuru O. Presence of Fibromyalgia Syndrome and Its Relationship with Clinical Parameters in Patients with Axial Spondyloarthritis. Pain Physician. 2019 Nov;22(6):E579–85.
9. Fernández-Carballido C, Sanchez-Piedra C, Valls R, Garg K, Sánchez-Alonso F, Artigas L, et al. Female Sex, Age, and Unfavorable Response to Tumor Necrosis Factor Inhibitors in Patients With Axial Spondyloarthritis: Results of Statistical and Artificial Intelligence–Based Data Analyses of a National Multicenter Prospective Registry. Arthritis Care Res. 2023 Jan;75(1):115–24.
10. Kohn SO, Azam A, Hamilton LE, Harrison SR, Graef ER, Young KJ, et al. Impact of sex and gender on axSpA diagnosis and outcomes. Best Pract Res Clin Rheumatol. 2023 Sep;37(3):101875.
11. Rusman T, Van Bentum RE, Van Der Horst-Bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. Rheumatology. 2020 Oct 1;59(Supplement_4):iv38–46.
12. Hanson A, Brown MA. Genetics and the Causes of Ankylosing Spondylitis. Rheum Dis Clin North Am. 2017 Aug;43(3):401–14.
13. Huang CH, Wei JCC, Chen CC, Chuang CS, Chou CH, Lin YJ, et al. Associations of the PTPN22 and CTLA-4 genetic polymorphisms with Taiwanese ankylosing spondylitis. Rheumatol Int. 2014 May;34(5):683–91.
14. Klavdianou K, Tsiami S, Baraliakos X. New developments in ankylosing spondylitis-status in 2021. Rheumatol Oxf Engl. 2021 Dec 24;60(Suppl 6):vi29–37.
15. Simone D, Al Mossawi MH, Bowness P. Progress in our understanding of the pathogenesis of ankylosing spondylitis. Rheumatol Oxf Engl. 2018 Aug 1;57(suppl_6):vi4–9.
16. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Care Res. 2019 Oct;71(10):1285–99.
17. Goswami RP, Sinha D, Chatterjee M, Bhadu D, Das S. Comparative Effectiveness of Tofacitinib and Adalimumab in Axial Spondyloarthritis: A Real-World Clinical Context Multicenter Study. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2024 Jun 1;30(4):e108–14.
18. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2023 Jan;82(1):19–34.
19. Danve A, O'Dell J. The ongoing quest for biomarkers in Ankylosing Spondylitis. Int J Rheum Dis. 2015 Nov;18(8):826–34.
20. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994 Dec;21(12):2281–5.
21. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. 2011 Jan;70(1):47–53.
22. Bedaiwi M, Sari I, Thavaneswaran A, Ayearst R, Haroon N, Inman RD. Fatigue in Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Analysis from a Longitudinal Observation Cohort. J Rheumatol. 2015 Dec;42(12):2354–60.
23. Calin A, Edmunds L, Kennedy LG. Fatigue in ankylosing spondylitis--why is it ignored? J Rheumatol. 1993 Jun;20(6):991–5.
24. van Tubergen A, Black PM, Coteur G. Are patient-reported outcome instruments for ankylosing spondylitis fit for purpose for the axial spondyloarthritis patient? A qualitative and psychometric analysis. Rheumatology. 2015 Oct 1;54(10):1842–51.
25. Rosenbaum JT, Pisenti L, Park Y, Howard RA. Insight into the Quality of Life of Patients with Ankylosing Spondylitis: Real-World Data from a US-Based Life Impact Survey. Rheumatol Ther. 2019 Sep;6(3):353–67.
26. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol. 2022 Nov 5;22(1):287.
27. McLachlan GJ. Cluster analysis and related techniques in medical research. Stat Methods Med Res. 1992;1(1):27–48.

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28. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994 Dec;21(12):2286–91.
29. Spoorenberg A, van der Heijde D, de Klerk E, Dougados M, de Vlam K, Mielants H, et al. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. J Rheumatol. 1999 Apr;26(4):980–4.
30. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984 Apr;27(4):361–8.
31. Anaconda Software Distribution [Internet]. Anaconda Documentation. Anaconda Inc.; 2020.
32. Wang R, Dasgupta A, Ward MM. Predicting Probability of Response to Tumor Necrosis Factor Inhibitors for Individual Patients With Ankylosing Spondylitis. JAMA Netw Open. 2022 Mar 1;5(3):e222312.
33. Lorenzin M, Ortolan A, Frallonardo P, Oliviero F, Punzi L, Ramonda R. Predictors of response and drug survival in ankylosing spondylitis patients treated with infliximab. BMC Musculoskelet Disord. 2015 Jul 24;16:166.
34. Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. RMD Open. 2015;1(1):e000017.
35. Pinto AS, Farisogullari B, Machado PM. Predictors of remission in people with axial spondyloarthritis: A systematic literature review. Semin Arthritis Rheum. 2022 Jul 27;56:152078.
36. Lee S, Kang S, Eun Y, Won HH, Kim H, Lee J, et al. Machine learning-based prediction model for responses of bDMARDs in patients with rheumatoid arthritis and ankylosing spondylitis. Arthritis Res Ther. 2021 Oct 9;23(1):254.
37. Benavent D, Franco-Gómez K, Plasencia-Rodriguez C, Novella-Navarro M, Bogas P, Nieto R, et al. Achievement rate and predictive factors of the recommended therapeutical target in patients with axial spondyloarthritis who remain on biological therapy: a prospective cohort study in Spain. BMJ Open. 2022 Apr 29;12(4):e057850.
38. Unal Enginar A. A comparison of the clinical characteristics and quality of life of male and female patients with non-radiographic axial spondyloarthritis. Int Immunopharmacol. 2023 Oct;123:110627.
39. Wright GC, Kaine J, Deodhar A. Understanding differences between men and women with axial spondyloarthritis. Semin Arthritis Rheum. 2020 Aug;50(4):687–94.
40. Li Z, van der Linden SM, Khan MA, Baumberger H, Zandwijk H van, Khan MK, et al. Heterogeneity of axial spondyloarthritis: genetics, sex and structural damage matter. RMD Open. 2022 May;8(1):e002302.
41. Roberts MJ, Hamrouni M, Linsley V, Moorthy A, Bishop NC. Exercise as an anti-inflammatory Therapy in Axial Spondyloarthritis Therapeutic Intervention (EXTASI) study: a randomized controlled trial. Rheumatol Adv Pract. 2024;8(2):rkae062.

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