Ref: Ro J Rheumatol. 2022;31(3)
DOI: 10.37897/RJR.2022.3.8

Disease activity and functional outcomes in non-radiographic spondyloarthritis versus ankylosing spondylitis – preliminary results

Ana-Maria Doca[1,2], Andreea Odobasu[1,2], Andreea Hortolomei[1,2], Mara Russu[1,2], Alexandra Popescu[1,2], Cristina Pomirleanu[1,2], Georgiana Strugariu[1,2], Codrina Ancuta[1,2]

[1]Rheumatology 2 Department, Clinical Rehabilitation Hospital Iasi, Romania
[2]"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

ABSTRACT

Introduction. Spondyloarthritis (SpA) represent a heterogeneous group of chronic inflammatory conditions sharing clinical, genetic, imaging and therapeutic features.

Objectives. To analyze the clinical and biological characteristics, disease activity and functional impact in non-radiographic axial SpA (nr-axSpA) versus ankylosing spondylitis (AS).

Material and method. Cross-sectional observational 12 months study on 46 patients with axial SpA; disease related parameters (clinical, biological, activity and functionality indices) and treatment options were compared in disease categories (nr-axSpA and AS).

Outcomes. AS was diagnosed in 73.9%, and nr-axSpA in 26.1% cases. The majority of patients with nr-axSpA were women (72% vs 28%), with a younger age at onset (35.2 ± 9.5 years vs 41 ± 0.6 years) and a shorter time to diagnosis (3 ± 0.5 vs 5.5 ± 3.2 years). C-reactive protein levels were significantly higher in AS compared to nr-axSpA (2.2 ± 0.5 vs 1.28 ± 0.7) ($p < 0.05$). However, there were no significant differences between activity (ASDAS-CRP: 3.4 ± 1.2 vs 3.2 ± 0.9; BASDAI: 5.8 ± 1.3 vs 5.6 ± 1.1) and functionality measures (BASFI: 5.8 ± 1.4 vs 5.7 ± 1.2) in ($p > 0.05$) in AS vs nr-axSpA.

Conclusions. Although nr-axSpA occurs frequently in women and may present with lower CRP levels, there are similar trends in disease activity and functional outcomes in both disease categories of the ax-SpA spectrum. Both nr-axSpA and AS patients experience high disease burden.

Keywords: non-radiographic axial spondyloarthritis, ankylosing spondylitis, disease burden, activity, functional outcome

INTRODUCTION

The spondyloarthritis (SpA) are a heterogeneous group of chronic immuno-inflammatory conditions that share a genetic (positive family history of SpA or related diseases, HLA-B27 positivity), clinical (chronic inflammatory back pain, peripheral arthritis, enthesitis, dactylitis), imaging (sacroiliitis, spondylitis) and therapeutic features (rapid and sustained response to nonsteroidal anti-inflammatory drugs). Furthermore, there are certain concept-related systemic manifestations such as acute anterior uveitis, inflammatory bowel disease, psoriasis, recurrent uro-genital or digestive infection considered key factors for defining disease outcomes and making the logical choice of SpA treatment [1].

The SpA group encompasses a broad spectrum of clinical entities with partially overlapping manifestations that can evolve at each stage to another distinct condition, generating controversies in definition and classification. In 1974, Moll and Wright first defined the SpA group with the following entities [2]: ankylosing spondylitis (AS), the prototype of the group; psoriatic arthritis, an entity with distinct clinical phenotypes associated with skin and/or nail psoriasis; reactive arthritis with the specific disease

Corresponding author:
Cristina Pomirleanu
E-mail: daniela.pomirleanu@umfiasi.ro

Article History:
Received: 27 September 2022
Accepted: 30 September 2022

subtype Reiter's syndrome, with the onset of musculoskeletal manifestations within 1 to 4 weeks after an uro-genital or digestive infection with specific germs; arthritis associated with inflammatory bowel diseases: ulcerative colitis and Crohn's disease; juvenile ankylosing spondylitis, with onset before the age of 16; undifferentiated spondyloarthritis, an entity that does not meet the diagnostic criteria for any of the previous entities [2].

In an effort to improve the definition and classification of SpA, ASAS (Assessment of SpondyloArthritis International Society) has developed classification criteria and has divided the group according to the type of joint damage into two main categories: SpA with predominantly axial manifestations (ax-SpA) comprising non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis, and SpA with predominantly peripheral manifestations accounting for all the other entities belonging to the groups [3].

According to the new ASAS 2009 criteria for the classification of axSpA, non-radiographic disease subset is defined as an axial spondyloarthritis with chronic inflammatory vertebral pain occurring in a genetically predisposed host (HLA-B27), with sacroiliac joint lesions detected only on magnetic resonance imaging (MRI) and no radiographic damage [3]. SA is mandatorily defined by evident radiographic structural damage in the sacroiliac joints (SIJ) (bilateral grade 2 or unilateral grade 3 or 4 SIJ changes), according to the modified New York criteria 1984 [4].

Although actually there is a clear consensus about the axSpA spectrum strengthening the paradigm of two distinct diseases, the question if nr-axSpA represents the early stage of AS or if is a totally distinct entity has raised controversies and debates. Re-examining the evidences supported the idea that a consistent number of patients do not end up developing radiographically detectable sacroiliitis [5]. Besides, it seems that 10-40% of cases with nr-axSpA will develop AS over a period of two to ten years [6], particularly if certain risk factors being able to stimulate and predict evolution are recognized: high CRP levels, positive HLA-B27, positive MRI and smoking [2].

The current study aimed to investigate the clinical and biological characteristics, activity and functional measures in patients with axial spondyloarthritis and to identify differences among patients with (radiographic spondyloarthritis or ankylosing spondylitis) and without (non-radiographic spondyloarthritis) radiological sacroiliitis.

MATERIAL AND METHODS

We conducted a cross-sectional observational study in a cohort of 46 consecutive patients with ax-SpA (fulfilling the ASAS 2009 classification criteria for ax-SpA or the modified 1984 New York diagnostic criteria for AS), who attended at least once an academic Outpatient Department in the North-East Romania (Rheumatology 2 Department, Clinical Rehabilitation Hospital of Iasi) between January 2020 and January 2021. We collected detailed data according to routine practice covering demographics, disease-related variables (duration, clinical phenotype, C-reactive protein levels) as well as medication (nonsteroidal anti-inflammatory drugs, biologics]. Disease activity measures such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP), as well as Bath Ankylosing Spondylitis Functional Index (BASFI) were also considered in all patients.

Each study participant signed an inform consent prior to the enrollment and the study protocol was approved by the local ethics committee.

The data collection and graphical representation were done using Microsoft Office 2010 Pack and the categorical variables were compared using the Person Chi-Square test. Although primary analysis was performed in all ax-SpA, in secondary analysis patients were stratified in AS or nr-axSpA and enrollment variables were further compared in disease subgroups. All statistical tests were 2-tailed and $p < 0.05$ was considered statistically significant.

RESULTS

Demographics and disease-related parameters

Table 1 summarizes the general characteristics of patients in our ax-SpA cohort and in subgroups of AS and nr-ax-SpA. Compared to AS, the majority of patients with nr-axSpA were female (72% vs 28%), with a younger age at onset (35.2 ± 9.5 vs 41 ± 0.6 years) and a shorter time interval until diagnosis (3 ± 0.5 vs 5.5 ± 3.2 years).

Extraspinal manifestations such as peripheral arthritis, enthesitis and acute anterior uveitis were more common in patients with AS than nr-axSpA. As expected, arthritis was present in both groups, with an evident preponderance for AS cases (35.2% vs. 8.3%). In the nr-axSpA group patients had little to no peripheral arthritis or extra-articular manifestations (8.3%).

CRP significantly higher in AS compared to nr-ax-SpA (2.2 ± 0.5 vs 1.28 ± 0.7) ($p < 0.05$).

It seems that patients in nr-axSpA group require NSAIDs more frequently as do those with AS (100% vs 73.5%), while more AS patients were prescribed Conventional synthetic disease modifying antirheumatic drugs (csDMARDs) (sulfasalazine) (26.4% vs 8.3%) for either peripheral arthritis or uveitis. In our cohort, biologics were given only in AS patients;

TABLE 1. Disease-related parameters in the studied population

Variable	ax-SpA 46 (100)	nr-axSpA 12 (26)	AS 34 (73.9)	P
Gender, n (%)				
Women	19 (41.3)	9 (72)	10 (28)	0.03
Men	27 (58.6)	3 (28	24 (72)	0.02
Age (years) mean + SD				
Women	40.7 ± 1.4	39.3 ± 12.1	42.1 ± 12.3	0.12
Men	44.15 ± 3.15	41 ± 2.7	47.3 ± 9.9	0.14
Disease onset (years) mean + SD	38.1 ± 2.9	35.2 ± 9.5	41 ± 0.6	0.14
Age at diagnosis (years) mean + SD	42 ± 3.7	38.3 ± 11.2	45.7 ± 11.5	0.12
Positive HLA B27 (n, %)	20 (43.4)	3 (25)	17 (50)	**<0.0001**
Extra-spinal features, n (%)				
Peripheral arthritis	13 (28.2)	1 (8.3)	12 (35.2)	0.57
Enthesitis	3 (6.5)	0	3 (8.8)	0.76
Acute anterior uveitis	3 (6.5)	0	3 (8.8	0.98
CRP (mg/L) mean + SD	1.7 ± 0.4	1.28 ± 0.7	2.2 ± 0.5	0.03
Disease activity mean + SD				
ASDAS-CRP	3.3 ± 0.5	3.4 ± 1.2	3.2 ± 0.9	0.16
BASDAI	5.7 ± 0.1	5.8 ± 1.3	5.6 ± 1.1	0.21
BASFI	5.7 ± 0.5	5.8 ± 1.4	5.7 ± 1.2	0.09
Treatment, n (%)				
NSAIDs	37 (80.4)	12 (100)	25 (73.5)	0.83
SSZ	10 (21.7)	1 (8.3)	9 (26.4)	0.75
iTNF	8 (17.3)	0 (0)	8 (23.5)	0.57
iIL-17A	1 (2.1	0 (0)	1 (2.9	0.89

SD, standard deviation; n: number; CRP, C reactive protein; ASDAS-CRP, Ankylosing Spondylitis Disease Activity score with CRP; BASDAI, The Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; NSAIDs, non-steroidal anti-inflammatory drugs; SSZ, sulfasalazine; iTNFα, TNFα inhibitors; IIL-17A, IL-17 inhibitors

none of those classified as nr-axSpA received nor TNF inhibitors neither IL-17A biologics, despite their active disease at the time of the enrollment visit.

We did not identify significant differences for age distribution, disease activity (BASDAI, ASDAS-CRP), functionality (BASFI) (Figure 1).

DISCUSSIONS

After the new 2009 ASAS classification criteria for axial spondyloarthritis were available, several studies compared nr-axSpA and AS trying to explore the burden of the axial SpA spectrum and to identify potential differences among genders in patients stratified according to the presence of radiological sacroiliitis [7,8].

We aimed to compare clinical (spinal and extraspinal) manifestations, systemic inflammation, disease activity and therapy of nr-axSpA patients versus AS ones in routine settings. Our results confirm the outcomes of earlier studies underpinning that patients with established AS and nr-axSpA do not differ greatly in many clinical variables [7,9]. However, we clearly identified several significant differences among patients belonging to nr-axSpA or AS.

Thus, we successfully showed that nr-axSpA subgroup had a higher prevalence in women and earlier disease onset. This is consistent with other studies, including the GESPIC cohort (GErman SPondyloarthritis Inception Cohort) [9]. Furthermore, Baraliakos et al. specified that this difference could appear because of the mechanical stress present more frequently in the male subgroup [9].

In addition, HLA-B27 was higher in AS patients than nr-axSpA based on available data in our cohort. This is in alignment with the REGISPONDER data base – the Spanish inception cohort (Registro Espanol de Espondiloartritis de la Sociedad Espanola de Reumatología) [10] and with data from PRESPOND (PREcision medicine in SPONdy-

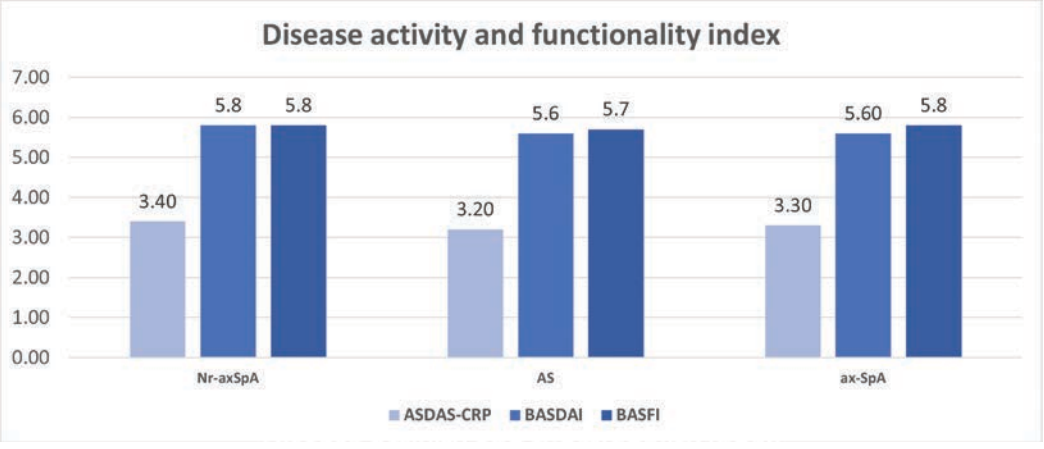

FIGURE 1. Disease activity and functionality index in the studied cohort
ASDAS-CRP: Ankylosing Spondylitis Disease Activity score with CRP; BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index

loarthritis for Better Outcomes and Disease Remission) registry in Singapore General Hospital [11].

We also explored severity and activity parameters in both subgroups and we do not identify any consistent differences between AS and nr-axSpA; similar trends in disease activity and functional indices were observed when patients were stratified by diagnosis of AS or nr-axSpA. This is in contrast with the GESPIC data, were AS is associated with a substantial burden of disease, due to advanced structural changes. Other studies had similar results, with a higher disease activity in AS [12,13]. Nonetheless, the extent of inflammation differs, with a higher CRP level in the AS group. This could change in the nr-axSpA development as analyzed by the ABILITY-1 clinical trial; the study revealed that an important number of nr-axSpA patients with negative or low CRP levels at baseline developed elevated CRP later, at week 12 [14]. Interestingly, extraspinal features such as enthesitis and acute anterior uveitis were not present in the nr-axSpA subgroup as shown in our study. A closer look to different other studies exposed a number of differences as follows: an equal prevalence in all extra-articular manifestations in the AS and nr-axSpA patients was found in some studies [15,16], contrasting with Winter JJ et al which reported that uveitis was slightly more prevalent in AS [17]. In the presented study, this difference could be based on the fact that the number of patients with nr-axSpA was lower than those with AS and the time frame until the onset of the disease and the diagnosis was small.

NSAIDs are the foundation stone in the treatment of AS and nr-axSpA. In the presented study csDMARDs and biologic therapy were used only in AS and this could be explained by the level of inflammation and the structural damage of the sacroiliac joint.

There are several potential limitations of our study. First, it was a retrospective analysis and, therefore, based only on available data routinely collected during a standard monitoring visit. Second, a significant proportion of AS patients were referred to our academic rheumatology department with active disease in order to assess activity and certify the recommendation of biologic; it may be difficult to assume that the CRP levels in AS would be at the same levels (higher that in nr-axSpA), if patients addressing only for habitual assessments, no for biologics. Third, our study was not a collaborative one; it was performed in a single rheumatology center, and, therefore, may not be representative of the entire spectrum of axSpA in our country.

CONCLUSION

Authors have successfully reinforced the results of other studies which claim that AS and nr-axSpA do not significantly differ clinically; indeed, nr-axSpA is broadly considered a disorder concerning more women than men, opposing AS that predictably emerges in men. Despite similar trends in disease activity, functional outcome in nr-axSpA is also important and both entities of the axial SpA spectrum are accountable for high disease burden.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Ancuța C, Pomîrleanu C. Principii de diagnostic și tratament în reumatologie. Iași: Gr. T Popa UMF Iași, 2019.
2. Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum.* 1973;3:55–78.
3. Sieper J, van der Heijde D, Landewé R, Brandt J, Burgos-Vagas R, Collantes-Estevez E et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis.* 2009;68:784–788.
4. 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. doi: 10.1002/art.1780270401. PMID: 6231933.
5. Mau W, Zeidler H, Mau R et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year follow up. *J Rheumatol.* 1988;15:1109–14.
6. Protopopov M, Poddubnyy D. Radiographic progression in non-radiographic axial spondyloarthritis. *Expert Rev Clin Immunol.* 2018;14:525–33.
7. Ping Seung Ong, Mohd R, Nur-Aida-Sabrina et al. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients in Malaysia. *The Egyptian Rheumatologist.* 2022;44(4):357-360.,
8. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H et al. The early disease stage in axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum.* 2009;60:717–27.
9. Baraliakos X, Listing J, von der Recke A et al. The natural course of radiographic progression in ankylosing spondylitis: differences between genders and appearance of characteristic radiographic features. *Curr Rheumatol Rep.* 2011;13:383–7.
10. Arévalo M, Gratacós Masmitjà J, Moreno M, Calvet J, Orellana C, Ruiz D et al.Influence of HLA-B27 on the ankylosing spondylitis phenotype: results fromthe REGISPONSER database. *Arthritis Res Ther.* 2018;20(1).
11. Hong C, Kwan YH, Leung YY et al. Comparison of ankylosing spondylitis and non-radiographic axial spondyloarthritis in a multi-ethnic Asian population of Singapore. *Int J Rheum Dis.* 2019;22,506–511.

12. Erol K, Gok K, Cengiz G et al. Extra-articular manifestations and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis. *Acta Reumatol Port.* 2018;43(1),32–39.
13. Wallman JK, Kapetanovic MC, Petersson IF et al. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients-baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. *Arthritis Res Ther.* 2015;17(1),378.
14. Baraliakos X, Sieper J, Chen S, Pangan AL, Anderson JK. Non-radiographic axial spondyloarthritis patients without initial evidence of inflammation may develop objective inflammation over time. *Rheumatology* (Oxford). 2017;56:1162–6.
15. Bubova K, Forejtova Š, Zegzulkova K et al. Cross-sectional study of patients with axial spondyloarthritis fulfilling imaging arm of ASAS classification criteria: baseline clinical characteristics and subset differences in a single centre cohort. *BMJ Open.* 2019;9(4):e024713.
16. Erol K, Gok K, Cengiz G et al. Extra-articular manifestations and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis. *Acta Rheumatol Port.* 2018;43:32–39.
17. de Winter JJ, van Mens LJ, van der Heijde D et al. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther.* 2016;18(1):196.