Practical Significance of Biomarkers in Axial Spondyloarthritis

Subjects: Rheumatology

Contributor: Alexandra-Diana Diaconu , Alexandr Ceasovschih , Victorița Șorodoc , Cristina Pomîrleanu , Cătălina Lionte , Laurențiu Șorodoc , Codrina Ancuța

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that can lead to ankylosis by secondary ossification of inflammatory lesions, with progressive disability and a significant impact on quality of life. It is also a risk factor for the occurrence of comorbidities, especially cardiovascular diseases (CVDs), mood disorders, osteoporosis, and malignancies. Early diagnosis and treatment are needed to prevent or decrease functional decline and to improve the patient's prognosis. In respect of axSpA, there is an unmet need for biomarkers that can help to diagnose the disease, define disease activity and prognosis, and establish personalized treatment approaches. The aim was to summarize the available information regarding the most promising biomarkers for axSpA. It can be classified and identified six core categories of biomarkers: (i) systemic markers of inflammation; (ii) molecules involved in bone homeostasis; (iii) HLA-B27 and newer genetic biomarkers; (iv) antibody-based biomarkers; (v) microbiome biomarkers; and (vi) miscellaneous biomarkers. Unfortunately, despite efforts to validate new biomarkers, few of them are used in clinical practice; these studies provide useful data that could aid in better disease management.

axial spondyloarthritis diagnosis disease activity prognosis

1. Axial Spondyloarthritis: Past, Present, and Future

Spondyloarthritis (SpA) comprises a group of chronic immune-mediated inflammatory conditions with overlapping clinical and genetic features but with substantial heterogeneity, as inflammation can affect peripheral and axial joints and also result in extraarticular manifestations (enthesitis, dactylitis, uveitis, inflammatory bowel disease, psoriasis) [1][2][3].

SpA comprises a spectrum of diseases with significant overlaps between SpA phenotypes, which can be classified according to the Assessment of Spondyloarthritis International Society (ASAS) 2009 classification criteria. These depend on where patients primarily experience symptoms in axial SpA (axSpA) with predominantly axial manifestations, including non-radiographic (nr-axSpA) and radiographic axSpA (r-axSpA) or ankylosing spondylitis (AS) and peripheral SpA (pSpA) with predominant peripheral involvement (psoriatic arthritis, reactive arthritis, enteropathic arthritis, juvenile-onset SpA, and undifferentiated SpA) [4]. While the spectrum of axSpA extends from early or mild disease through severe or late disease with erosive damage in the sacroiliac joints, this arbitrary division of nr-axSpA and r-axSpA is becoming less clinically relevant.

The symptoms of axSpA create a significant burden for both patients and society. The major disease feature is the progression to ankylosis by secondary ossification of inflammatory lesions, with progressive disability and a significant impact on quality of life.

AxSpA is also a risk factor for the occurrence of comorbidities, especially cardiovascular diseases (CVDs), mood disorders, osteoporosis, and malignancies, which shows that axSpA has a systemic character and influences patient health in a complex manner [2]. All these characteristics affect quality of life and, because all comorbidity types correlate with axSpA, early diagnosis and treatment are needed to prevent or decrease functional decline and improve the patient's prognosis.

2. AxSpA and Biomarkers

According to the World Health Organization, a biomarker is a chemical, physical, or biological indicator of disease presence, activity, or severity, which can provide vital information. In respect of axSpA, there is an unmet need for biomarkers that can help to diagnose the disease, define disease activity and prognosis, and establish personalized treatment approaches [5].

Despite the progress made in the concept of axSpA, its identification remains challenging, frequently resulting in a diagnostic delay for patients. Ideally, the diagnosis should be made before the development of radiographic sacroiliitis, but currently the most sensitive imaging diagnosis method is magnetic resonance imaging (MRI), which is costly and not widely available [2].

AxSpA disease activity is monitored using the following scores: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Activity Score (ASDAS), which may be subjective. Disease activity is also monitored by measuring of one of the most common inflammatory biomarkers, C-reactive protein (CRP), which is insensitive for this disease [6].

Although the range of effective modern drugs for axSpA has expanded in recent decades, therapeutic decisions and the response to specific therapies remain challenges in current practice, and further research is therefore required. Adequate evaluation of disease activity, radiographic progression, response to treatment and identification of negative prognostic factors can improve the therapeutic decision. In addition, data regarding the axSpA prognosis obtained in the early disease stages will improve therapeutic management [2].

The aim of was to summarize available information regarding the most promising biomarkers for axSpA. The researchers further refer to six core categories of biomarkers: (i) systemic markers of inflammation; (ii) molecules involved in bone homeostasis; (iii) HLA-B27 and newer genetic biomarkers; (iv) antibody-based biomarkers; (v) microbiome biomarkers; and (vi) miscellaneous biomarkers (**Table 1**, **Figure 1**). Furthermore, the association between biomarkers and diagnosis, disease activity, structural damage, and treatment response are described below.

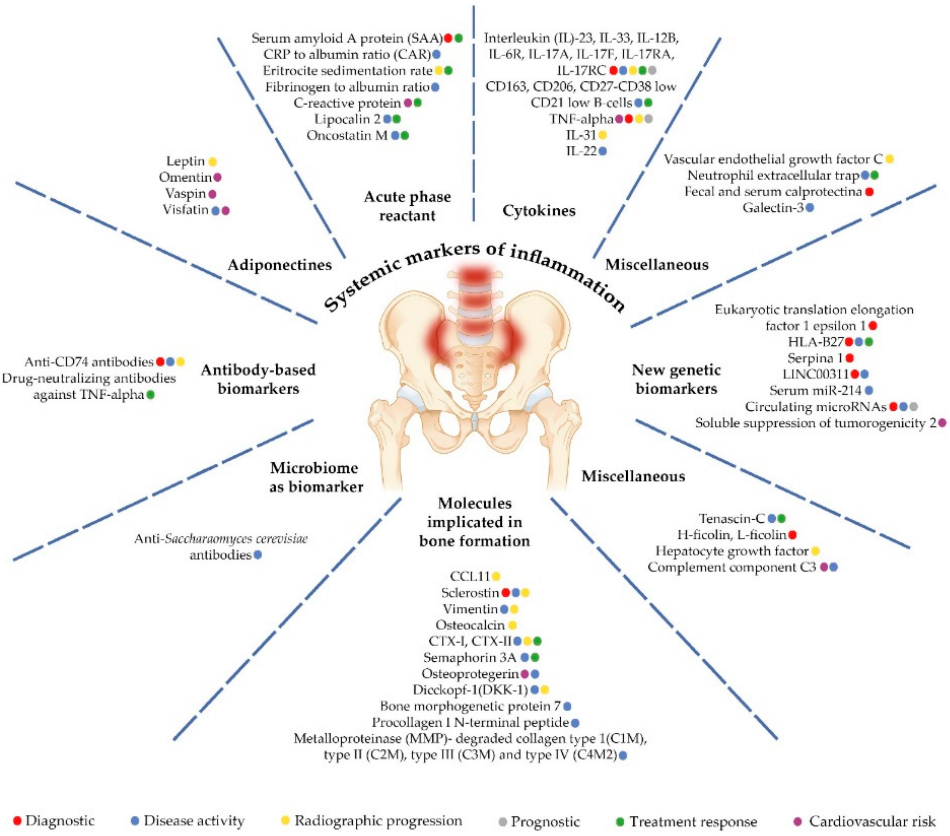

Figure 1. Biomarkers significance in axial spondiloarthtitis.

Table 1. Biomarkers significance in axial spondyloarthritis.

Biomarker	Predictability	Study type	Reference
Anti-CD74 antibodies	Positive association with diagnosis and disease activity.	Cross-sectional study	2021, Marwa Mahmoud Abdelaziz [7]
	Positive association with radiographic progression.	Prospective study	2021, Lan Do [8]
	Positive association with diagnosis.	Prospective study	2019, Nelly R. Ziade [9]
	Negative association with diagnosis.	Prospective study	2018, Janneke J. de Winter [10]
	Positive association with diagnosis.	Prospective study	2020, Chao-Jun Hu [11]
Bone morphogenetic protein 7 (BMP-7), sclerostin, dicckopf-1 (DKK-1)	Positive association with disease association	Prospective multicenter study	2021, Elise Descamps [12]
C-reactive protein (CRP)	Positive association with cardiovascular risk	Retrospective analysis	2022, Luca Navarini [13]

Biomarker	Predictability	Study type	Reference
	Positive association with treatment response Positive association with treatment response Positive association with treatment response	Prospective study Case-control study Cross-sectional study	2019, Xenofon Baraliakos [14] 2020, Xu Yuansheng [15] 2018, Björn Sundström [16]
C-C motif chemokine ligand 11 (CCL11)	Positive association with radiographic progression	Cross-sectional study	2018, Dong Hyun Sohn [17]
CD163, CD206	Positive association with disease activity, treatment response	Prospective study	2018, Line Dam Heftdal [18]
CD27-CD38^{low}CD21^{low} B cells	Positive association with disease activity	Cross-sectional study	2021, Rick Wilbrink [19]
circRNA hsa_circ_0079787	Positive association with diagnosis, disease activity	Cross-sectional study	2020, Qing Luo [20]
Circulating microRNAs	Positive association with disease activity Positive association with diagnosis and disease activity	Prospective study Cross-sectional study	2020, Qing Luo [20] 2018, Carlos Perez-Sanchez [21]
Complement component C3	Positive association with disease activity and cardiovascular risk	Cross-sectional study	2020, Ivan Arias de la Rosa [22]
CRP to albumin ratio (CAR)	Positive association with disease activity Positive association with disease activity	Retrospective study Cross-sectional study	2021, Zheng Zhong [23] 2021, Melih Pamukcu [24]
Dickkopf homologue-1 (Dkk-1)	Positive association with radiographic progression	Prospective study	2019, Zhonghai Zhao [25]
Bone morphogenetic proteins (BMPs) and Dkk-1	Positive association with disease activity	Prospective study	2018, Hsien-Tzung Liao [26]
Drug-neutralizing Antibodies against TNF-*α*	Positive association with treatment response	Cross-sectional study	2020, Krasimir Kraev [27]

Biomarker	Predictability	Study type	Reference
ERAP1 (rs2287987, rs30187, rs27044), ERAP2 (rs2248374)	Positive association with diagnosis	Case-control study	2019, Andrzej Wiśniewski [28]
Erythrocyte sedimentation rate (ESR)	Positive association with radiographic progression	Retrospective study	2018, Kwi Young Kang [29]
ESR + Interleukin (IL)-6	Positive association with treatment response	Prospective study	2019, Yidian Dong [30]
Eukaryotic translation elongation factor 1 epsilon 1 (*EEF1E1*)	Positive association with diagnosis	Prospective study	2019, Xutao Fan [31]
Fecal calprotectina and anti-*Saccharaomyces cerevisiae antibodies* (ASCA)	Positive association with disease activity	Cross-sectional study	2019, Tor Olofsson [32]
Fibrinogen-to-albumin ratio (FAR)	Positive association with disease activity	Retrospective study	2020, Meng Liu [33]
Galectin-3	Positive association with disease activity	Prospective study	2019, Ming-Yu Cao [34]
Galectin-3, soluble suppression-of-tumorogenity-2 (sST2) (cardiac fibrosis), hsCRP	Positive association with cardiovascular risk	Prospective study	2018, Demet Ozkaramanli Gur [35]
H-ficolin, L-ficolin	Positive association with diagnosis	Cross-sectional cohort	2020, Anne Troldborg [36]
Hepatocyte growth factor (s-HGF)	Positive association with radiographic progression	Prospective cohort study	2021, Anna Deminger [37]
	Positive association with radiographic progression	Prospective study	2019, Liset Torres [38]
HLA B-27 antigen	Positive association with diagnosis	Prospective study	2019, Nelly Ziade [39]
	Positive association with diagnosis	Prospective study	2018, Chong Seng Edwin Lim [40]
	Positive association with diagnosis	Prospective study	2021, Henriëtte M Y de Jong [41]
Interleukin (IL)-31	Positive association with radiographic progression	Longitudinal prospective cohort study	2018, Nicolas Rosine [42]
IL-33	Positive association with disease activity and	Prospective study	2021, Milena Iwaszko [43]

Biomarker	Predictability	Study type	Reference
	treatment response		
IL-12B and IL-6R	Positive association with diagnosis and prognosis	Prospective cohort study	2018, Wen-Feng Ruan [44]
IL-22	Positive association with diagnosis	Retrospective study	2022, Michal Sagiv [45]
IL-17 **IL-23 and IL-17**	Positive association with diagnosis Positive association with diagnosis	Cross-sectional study Case-control study	2020, Dalia S. Saif [46] 2018, Jacob Sode [47]
Leptin	Positive association with radiographic progression Positive association with radiographic progression	Longitudinal prospective study Prospective study	2017, Ji-Heg Park [48] 2019, Judith Rademacher [49]
Leptin + high molecular weight adiponectin + VEGF	Positive association with radiographic progression	Cross-sectional study	2019, Judith Rademacher [49]
LINC00311	Positive association with diagnosis and disease activity	Prospective study	2019, Hongfa Zhong [50]
Lipocalin 2 (LCN 2), Oncostatin M (OSM)	Positive association with disease activity and treatment response	Longitudinal observational study	2021, Florence W.L Tsui [51]
Metalloproteinase (MMP)-degraded collagen type I (C1M), type II (C2M), type III (C3M), and type IV (C4M2)	Positive association with disease activity	Prospective cohort study	2019, Markéta Husšáková [52]
Neutrophil extracellular trap (NET)	Positive association with disease activity and treatment response	Cross-sectional study, case report	2020, Patricia Ruiz-Limon [53]
Omentin-1	Positive association with cardiovascular risk	Prospective study	2020, Fernanda Genre [54]
Osteoprotegerin (OPG) and sclerostin (SCL)	Positive association with cardiovascular risk	Prospective study	2018, Fernanda Genre [55]
Pentraxin 3	Positive association with disease activity	Cross-sectional study	2018, Renato Nisihara [56]
Procollagen I N-terminal peptide	Positive association with disease activity	Cross-sectional study	2022, Xuegang Li [57]

Biomarker	Predictability	Study type	Reference
Sclerostin and antisclerostin antibody	Positive association with gastrointestinal risk Positive association with diagnosis Positive association with radiographic progression	Prospective study Case-control study Prospective study	2018, Michele Maria Luchetti [58] 2018, Perrota Fabio Massimo [59] 2019, Judith Rademacher [49]
Semaphorin 3A (Sema 3A)	Positive association with disease activity Positive association with treatment response	Prospective study Prospective study	2019, Hsien-Tzung Liao [60] 2017, Fabio Massimo Perrotta [61]
Serum amyloid A1 (SAA1)	Positive association with diagnosis	Prospective study	2020, Shijia Liu [62]
Serum calprotectin	Positive association with disease activity Positive association with treatment response Positive association with cardiovascular risk Positive association with radiographic progression	Prospective study Prospective study Prospective study Prospective study	2020, Matthias Jarlborg [63] 2019, Hua Hu [64] 2018, Fernanda Genre [65] 2022, Judith Rademacher [66]
Serum miR-214	Positive association with disease activity	Prospective study	2019, Hyun Yi Kook [67]
Tenascin-C (TNC)	Positive association with disease activity Positive association with disease activity	Prospective study Prospective study	2020, Kristyna Bubova [68] 2018, Latika Gupta [69]
Vaspin	Positive association with cardiovascular risk	Prospective study	2021, Javier Rueda-Gotor [70]
Vimentin	Positive association with radiographic progression	Prospective study	2019, Anne Sofie Siebuhr [71]
Visfatin	Positive association with cardiovascular risk Positive association with disease activity	Prospective study Prospective study	2021, Rabia Aydogan Baykara [72]

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Biomarker	Predictability	Study type	Reference
			2022, Judith Rademacher [66]

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