

Pathogenesis, Clinical Spectrum, and Assessment of Spondyloarthritis: A Literature Review

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ABSTRACT

Spondyloarthritis (SpA) is a family of chronic inflammatory rheumatic diseases that share inflammatory back pain, sacroiliitis, peripheral arthritis, enthesitis, dactylitis, extra-articular involvement, absence of rheumatoid factor, and a strong association with HLA-B27. Its presentation varies between patients and subtypes, and this variability can delay diagnosis by several years. This narrative review summarizes the pathogenesis, clinical spectrum, classification, and assessment of SpA. HLA-B27 may promote disease through the presentation of arthritogenic peptides, protein misfolding with endoplasmic reticulum stress, and the formation of heavy-chain homodimers. Mechanical stress at the entheses, gut dysbiosis, and adipokines released by excess adipose tissue add to the inflammatory load. These pathways converge on the interleukin-23/interleukin-17 axis and tumor necrosis factor-alpha, which sustain inflammation in the entheses and bone marrow, cause trabecular bone loss, and later favor new bone formation through Wnt and bone morphogenetic protein signaling. Ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and arthritis associated with inflammatory bowel disease remain the classic subtypes, which the Assessment of SpondyloArthritis international Society (ASAS) now groups into axial and peripheral forms. Beyond the spine and joints, SpA can affect the eyes, heart, lungs, kidneys, liver, and gallbladder. Reported frequencies vary between cohorts, and Indonesian data come from small single-center series. ASAS classification criteria, inflammatory markers, the complete blood count, and the Ankylosing Spondylitis Disease Activity Score provide a structured framework for recognition and follow-up. Multicenter studies should now define the clinical pattern of SpA in Indonesia.

Keywords: spondyloarthritis; HLA-B27; enthesitis; sacroiliitis; ASAS classification criteria; ASDAS

INTRODUCTION

Spondyloarthritis (SpA) covers several chronic inflammatory rheumatic diseases that differ in presentation but share a common set of features: inflammatory back pain, inflammation of the sacroiliac joints (sacroiliitis), peripheral arthritis, enthesitis, dactylitis, extra-articular manifestations, a negative rheumatoid factor, and a frequent association with HLA-B27 [1]. The Assessment of SpondyloArthritis International Society (ASAS) groups patients by their dominant presentation into axial SpA, which covers ankylosing spondylitis (AS) and non-radiographic axial SpA, and peripheral SpA [2,3]. The traditional subtypes remain in use in clinical practice and in much of the published literature: AS, psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), and undifferentiated SpA.

The variable presentation of SpA delays its diagnosis. In a survey of 1,080 patients with AS, the mean

interval between symptom onset and diagnosis was 8.5 years in HLA-B27-positive patients and 11.4 years in HLA-B27-negative patients [4]. Disease expression also differs between populations [5]. In the worldwide ASAS-PerSpA study of 4,465 patients from 24 countries, 57% of patients had a history of peripheral joint disease; the proportion reached 80% in Latin America, and Asian patients showed the highest frequency of hip and shoulder involvement [6].

Indonesian data are scarce. A cross-sectional study of 40 patients at Dr. Soetomo General Academic Hospital, Surabaya, found radiographic sacroiliitis in 70% and inflammatory back pain in 65%, while dactylitis (7.5%) and uveitis (2.5%) were uncommon [7]. A single-center series of this size cannot describe the national picture, and clinicians who know the full range of the disease are better placed to recognize it early. This review summarizes the pathogenesis, pathophysiology, clinical subtypes, musculoskeletal

and extra-articular manifestations, classification criteria, laboratory evaluation, and disease activity assessment of SpA.

METHODS

This article is a narrative literature review. The authors identified sources mainly through PubMed and ScienceDirect and located regional publications and other references through Google Scholar and the reference lists of retrieved articles. The sources comprise ASAS classification and outcome publications, clinical cohort and registry studies, experimental studies in humans and animal models, review articles, StatPearls chapters from the NCBI Bookshelf, an online radiology reference, and rheumatology textbooks published between 1972 and 2024. The authors selected sources for their relevance to SpA pathogenesis, pathophysiology, clinical subtypes, clinical manifestations, classification, laboratory evaluation, and disease activity assessment, and synthesized the findings by theme. The review did not include a formal quality appraisal or a meta-analysis.

Pathogenesis

SpA develops from the combined effects of genetic susceptibility, immune dysregulation, biomechanical stress, environmental exposure, and metabolic factors [8]. The strongest genetic risk factor is HLA-B27, a major histocompatibility complex (MHC) class I molecule that presents peptide antigens on the cell surface to the receptors of CD8⁺ T lymphocytes [9]. Up to 95% of patients with AS carry HLA-B27 [5].

• HLA-B27 and Other Genetic Factors

Three main hypotheses link HLA-B27 to disease [8]. The arthritogenic peptide hypothesis proposes that HLA-B27 presents self-peptides that resemble microbial peptides, so that cytotoxic CD8⁺ T cells primed against a microbe go on to attack joints and other tissues. Synovial fluid studies support this idea. A peptide derived from type VI collagen stimulated HLA-B27-restricted CD8⁺ T cells in four of seven synovial fluid samples from patients with AS [10]. A second self-peptide, residues 400–408 of vasoactive intestinal peptide receptor 1 (VIP1R), shares sequence features with an epitope of the Epstein–Barr virus latent membrane protein 2 (LMP2), and CD8⁺ T cells from patients with AS respond to it [11]. Molecular mimicry of this kind may turn an antimicrobial T-cell response against the host.

The misfolding hypothesis rests on the slow folding of HLA-B27 heavy chains, which then accumulate in the endoplasmic reticulum (ER). The resulting ER stress activates the unfolded protein response and autophagy, which increases the production of pro-inflammatory cytokines such as interleukin (IL)-17, IL-23, and interferon-gamma (IFN- γ) [8]. The third hypothesis concerns HLA-B27 heavy chains that pair with each other on the cell surface. These homodimers act as pro-inflammatory ligands and can trigger humoral or cell-mediated autoimmune responses [8].

HLA-B27 subtypes differ in risk. B*2705 and B*2704 show a strong association with SpA, whereas B*2709 does not appear to confer risk. B*2709 differs from B*2705 at a single amino acid, residue 116, a change thought to alter the conformation of the molecule and the T-cell response it elicits [12]. Genes outside the MHC also contribute. *ERAP1* encodes an aminopeptidase of the ER that trims peptides before they load onto MHC class I molecules, which assemble from a heavy chain and β_2 -microglobulin inside the ER before export to the cell surface. Accumulation of misfolded proteins in this compartment triggers the unfolded protein response, a pro-inflammatory signal that feeds the IL-23/IL-17 cascade [13].

• *Mechanical Stress, the Gut–Joint Axis, and Infection*
Biomechanical stress at the entheses shapes the earliest tissue damage in SpA. Repeated microtrauma at tendon insertions activates the innate immune system and releases local pro-inflammatory mediators [8]. Gut dysbiosis provides a second trigger through the gut–joint axis. Changes in the intestinal microbiome weaken the mucosal barrier, bacterial antigens cross into the gut wall and activate mucosal immune cells, and these cells then migrate to the joints and entheses [8].

Barrier failure at other sites has a similar effect. Skin lesions in psoriasis and mucosal damage in Crohn's disease expose the immune system to bacterial antigens. HLA-B27 itself may prolong this exposure: human monocytic cells expressing HLA-B27 allowed longer intracellular survival of *Salmonella enteritidis* than control cells, which points to less efficient clearance of intracellular bacteria in HLA-B27 carriers [14].

• Adipose Tissue and Metabolic Factors

Adipose tissue functions as an active endocrine organ. It secretes bioactive molecules called adipokines, including leptin, resistin, and visfatin, and obesity raises the output of these pro-inflammatory mediators. Adipokines interact with immune cells and amplify systemic inflammation, so a high body mass index adds an inflammatory burden to the mechanical load it already places on weight-bearing joints [15].

• A Shared Inflammatory Pathway

Genetic, mechanical, environmental, and metabolic triggers converge on two cytokine systems: the IL-23/IL-17 axis and tumor necrosis factor- α (TNF- α). These cytokines sustain inflammation in the synovium and entheses and stimulate abnormal bone remodeling [8].

Pathophysiology: Inflammation, Bone Loss, and New Bone Formation

SpA results from interactions between predisposing genes, microbial triggers, bone marrow inflammation, and the response of bone [13]. Two processes define the disease. The first is inflammation of the bone marrow (osteitis) and of the entheses (enthesitis); the second is the formation of new bone, which leads to ankylosis and loss of mobility. In advanced disease,

ankylosis spreads along the spine and produces the radiographic “bamboo spine” [13].

The inflammatory target of SpA differs from that of rheumatoid arthritis (RA). In RA, inflammation targets the synovial membrane, whereas in SpA it centers on the entheses and the bone marrow [16]. Entheses, the sites where ligaments and tendons attach to bone, are rich in fibrocartilage and exposed to repeated mechanical stress [17]. Inflamed entheses and marrow contain infiltrates of T cells, B cells, and macrophages. Under the influence of receptor activator of nuclear factor- κ B ligand (RANKL), macrophages differentiate into bone-resorbing osteoclasts. Activated macrophages and T cells release large amounts of TNF- α , and T cells also produce IL-17, which amplifies the inflammatory cascade.

Bone marrow inflammation causes loss of trabecular bone inside the vertebral bodies and raises the risk of osteoporosis and vertebral fracture in patients with SpA. HLA-B27 transgenic rats, an animal model of SpA, show the same pattern, with reduced bone mineral density and a higher ratio of RANKL to osteoprotegerin expression [18].

New bone formation distinguishes SpA from RA. Syndesmophytes grow across the intervertebral spaces and the sacroiliac joints, causing spinal stiffness and thoracic kyphosis. Exaggerated responses to mechanical stress and inflammation at the entheses drive this process, and bony spurs can form without a preceding erosion; in experimental arthritis, blockade of TNF- α and RANKL protected bone from erosion but failed to stop spur formation [19]. Osteoblasts lay down most of the new bone through endochondral ossification, a sequence resembling long-bone growth in which hypertrophic chondrocytes deposit type X collagen, while membranous ossification makes a smaller contribution [20].

Differentiated osteoblasts synthesize type I collagen and osteocalcin, which build the bone matrix and regulate its mineralization. Prostaglandin E₂, bone morphogenetic proteins (BMPs) acting through Smad proteins, and the Wnt/ β -catenin pathway control osteoblast differentiation. In SpA, low expression of the natural Wnt inhibitors Dickkopf-1 (DKK-1) and sclerostin leaves Wnt signaling unchecked and favors bone formation [13]. Animal work supports this model: DKK-1 acts as a master regulator that determines whether an inflamed joint loses bone or forms new bone [21].

Clinical Subtypes

Classic descriptions of SpA center on four differentiated subtypes, and patients who fit none of them receive a diagnosis of undifferentiated SpA. ASAS now places these subtypes within the axial and peripheral groups according to the dominant presentation [2,3].

• Ankylosing Spondylitis

AS is a chronic inflammatory disease that targets the

spine. It presents chronic back pain and progressive stiffness and can involve the sacroiliac joints, peripheral joints, and entheses [22]. AS accounted for 69.1% of 275 patients in a French tertiary-care SpA cohort, in which men predominated [23]. Patients report reduced spinal mobility, postural change, buttock and hip pain, peripheral arthritis, enthesitis, and dactylitis. Inflamed tissue contains CD4⁺ and CD8⁺ T cells and macrophages, and cytokines such as TNF- α and transforming growth factor-beta (TGF- β) promote fibrosis and ossification at the inflamed sites. Ossification of the spine limits movement and alters posture, with hyperkyphosis and, in time, ankylosis that produces the bamboo spine [22].

The modified Schober test and magnetic resonance imaging (MRI) are the tools most used to evaluate AS. The Schober test measures lumbar flexion: the examiner marks a 10 cm segment over the lumbar spine, and an increase of less than 5 cm during maximal forward bending indicates restricted lumbar mobility. MRI is the most sensitive imaging method and can show bone marrow edema, erosions, fatty infiltration, new bone formation, and ankylosis [22].

• Psoriatic Arthritis

PsA has both articular and periarticular features. These include oligoarticular or polyarticular peripheral arthritis, enthesitis, dactylitis, tenosynovitis, and axial disease in the form of asymmetric sacroiliitis and spondylitis. Extra-articular features include psoriasis of the skin and nails and uveitis, which in PsA tends to be chronic and bilateral and can involve the posterior segment of the eye [24]. Psoriasis was present in 30% of the Surabaya cohort [7].

• Reactive Arthritis

ReA is an inflammatory arthritis that follows a gastrointestinal infection, for example with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, or *Clostridioides difficile*, or a genitourinary infection with organisms such as *Chlamydia trachomatis*, *Mycoplasma hominis*, or *Ureaplasma urealyticum*. The classic triad of arthritis, urethritis, and conjunctivitis gave the condition its former name, Reiter syndrome [25]. Patients may first have fatigue and fever, followed by an asymmetric oligoarthritis that favors the lower limbs [25]. ReA made up 1.8% of the French SpA cohort [23].

• Enteropathic Arthritis

Enteropathic arthritis, or IBD-associated SpA, accompanies Crohn's disease and ulcerative colitis. The two conditions share immunopathological mechanisms, including dysregulation of innate and adaptive immunity and dysbiosis of the gut microbiota. Chronic intestinal inflammation spills over into a systemic response that reaches the joints and other structures, and HLA-B27, together with mediators such as IL-23, IL-17, and TNF- α , favors the development of peripheral or axial arthritis in patients with IBD [26]. Patients present with axial features (sacroiliitis and inflammatory back pain)

and peripheral features (enthesitis and dactylitis) alongside bowel symptoms. Chronic abdominal pain with non-bloody diarrhea suggests Crohn's disease, whereas bloody diarrhea with mucus suggests ulcerative colitis [27]. In the French cohort, 8.4% of patients had this subtype, with a balanced sex distribution [23].

Axial and Peripheral Musculoskeletal Manifestations

Table 1 lists the frequencies of selected manifestations reported in the studies reviewed here.

• *Inflammatory Back Pain*

Inflammatory back pain (IBP) is the most characteristic symptom of SpA and was present in 65% of the Surabaya cohort [7]. Patients describe a dull pain in the lower back, buttocks, or hips that lasts longer than three months and comes with morning stiffness of 30 minutes or more. The pain responds to nonsteroidal anti-inflammatory drugs (NSAIDs) [28], and 87.5% of the Surabaya patients reported a good NSAID response [7]. Early in the disease, inflammatory markers and radiographs may still be normal, so the recognition of IBP depends on a careful history [28].

ASAS experts proposed criteria to identify IBP in patients with chronic back pain. IBP is present when at least four of the following five features apply: age at onset below 40 years, insidious onset, improvement with exercise, no improvement with rest, and pain at night with improvement upon getting up [29].

• *Sacroiliitis*

Sacroiliitis is a hallmark of axial SpA and one of the core elements of the ASAS classification criteria. It causes progressive pain in the lower back or buttocks that tend to appear at night, comes with morning stiffness, and eases with activity [30]. Radiographic sacroiliitis was present in 70% of the Surabaya cohort [7]. In early axial SpA, sacroiliac pain may be atypical, intermittent, or unilateral and may radiate to the groin, lower abdomen, greater trochanter, or lower limb, reflecting the variable innervation of the joint and the involvement of surrounding structures. Palpation and provocation maneuvers, such as the pelvic rock test, Patrick's test, and Gaenslen's maneuver, can reproduce sacroiliac pain. Radiographs show structural changes in the form of erosions, sclerosis, and joint space narrowing [30].

• *Anterior Chest Wall Pain*

In a French cohort of 275 patients with SpA, 102 (37.1%) reported chest wall pain related to their disease, and in 3.6% this pain was the first symptom of SpA [23]. Most patients felt the pain in the upper chest, with an acute onset and worsening on breathing and arm movement; 41% had pain at night. Flares lasted about five weeks and recurred in 75% of patients. NSAIDs were effective in 49.3% of cases and anti-TNF agents in 80.0% [23].

Possible sources of this pain include inflammation of the costosternal and sternoclavicular joints,

involvement of the ribs and sternum, enthesitis of the chest wall, and restricted chest expansion. Clinicians must exclude cardiac and pulmonary causes before attributing chest pain to SpA. Computed tomography (CT) can show joint space narrowing, erosions, and sclerosis at the sternoclavicular and upper sternocostal joints, and MRI can show bone marrow edema, joint effusion, and synovitis at the sternoclavicular and manubriosternal joints [23].

• *Peripheral Arthritis*

Peripheral arthritis affected 45% of the Surabaya cohort [7]. In ASAS-PerSpA, 57% of all patients had a history of peripheral joint disease: 36% of those with axial SpA, 90.8% of those with PsA, and 94.7% of those with peripheral SpA [6]. The typical pattern is an asymmetric oligoarthritis that favors large lower-limb joints such as the knees and ankles, although the wrists, elbows, and shoulders can be involved as well. HLA-B27 is present in 27% to 47% of patients with peripheral-predominant SpA. On examination, the affected joints show redness, warmth, tenderness, and a limited range of motion [31].

• *Dactylitis*

Dactylitis is diffuse swelling of an entire finger or toe, the "sausage digit," in which inflammation can involve the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints [32]. It can appear early in the disease and is a hallmark of PsA, in which it has been reported in up to 49% of patients [33]. Dactylitis affected 7.5% of the Surabaya cohort [7]. In ASAS-PerSpA, 15% of all patients had a history of dactylitis, ranging from 6.0% of those with axial SpA to 37.0% of those with PsA [6]. Dactylitis tends to be asymmetric and can affect several digits at once. Some reports describe a predilection for the toes [32], but ASAS-PerSpA found fingers (62%) and toes (59%) involved at similar rates [6]. The swollen digit combines tenosynovitis, synovitis, soft tissue edema, and, in some patients, bone erosion, which radiography, ultrasonography, or MRI can demonstrate [32].

Extra-Articular Manifestations

• *Enthesitis*

Entheses lie outside the joint cavity, at the sites where tendons, ligaments, and joint capsules insert into bone. Inflammation at these sites is a pathological signature of SpA and a major source of pain [34]. Heel enthesitis was recorded in 40% of the Surabaya cohort [7], and 44% of patients in ASAS-PerSpA had a history of enthesitis, with the heel as the first affected site in 69% [6]. Enthesitis has a mechanical and an inflammatory component. Mechanical stress explains its predilection for the weight-bearing lower limbs, and IL-23 and IL-17 activate T cells and innate immune cells at the enthesis, leading to local inflammation, tissue damage, and bone remodeling [32,34].

Enthesitis presents as localized tenderness at sites such as the Achilles tendon insertion, plantar fascia, patella, tibial tuberosity, metatarsal heads, base of the fifth metatarsal, iliac crest, anterior superior iliac

spine, tarsal region, greater trochanter, and lateral epicondyle. The diagnosis rests on the history and on physical examination findings of tenderness and redness at these sites [32].

- *Acute Anterior Uveitis*

Acute anterior uveitis (AAU), inflammation of the anterior uveal tract, is the most frequent ocular manifestation of SpA [32]. Its reported frequency ranges from 2.5% in the Surabaya cohort [7] to 28% in the French cohort [23]. HLA-B27 status influences the risk: in the survey of patients with AS described above, 41% of HLA-B27-positive and 26% of HLA-B27-negative patients reported AAU [4]. AAU tends to be unilateral and recurrent, and patients present with redness, pain, blurred vision, excessive tearing, photophobia, and miosis [32].

- *Cardiac Involvement*

Cardiac disease linked to AS includes aortitis, aortic valve disease, conduction disturbances, cardiomyopathy, and ischemic heart disease [35]. Pericarditis, inflammation of the thin sac that surrounds the heart, is less common. It can cause chest pain, pericardial effusion, and impaired cardiac function. Erkan et al. described recurrent pleural and pericardial effusion without lung parenchymal disease in a patient with AS, who responded to prednisolone [36]. On a chest radiograph, a pericardial effusion enlarges the cardiothoracic ratio and gives the cardiac silhouette a rounded, flask-like shape [37].

- *Pulmonary and Pleural Involvement*

In the lungs, AS can cause upper-lobe fibrosis, interstitial lung disease, restrictive ventilatory impairment from a rigid chest wall, sleep apnea, and spontaneous pneumothorax [35]. Lung involvement is rare, and its most common form is upper-lobe fibrocavitary disease [36]. Pleuritis causes sharp chest pain that worsens with breathing or coughing and may progress to pleural thickening, a finding that plain chest radiographs can detect [36,38].

- *Renal Involvement*

Renal disease in SpA takes three main forms: IgA nephropathy, reduced renal function, and nephrolithiasis. Deposition of immunoglobulin A in the glomeruli causes local inflammation and glomerular injury. Chronic inflammation can promote arteriosclerosis and endothelial dysfunction that reduce renal function, long-term NSAID use carries a risk of nephrotoxicity, and altered calcium metabolism together with systemic inflammation may favor stone formation [39].

In a retrospective study of 350 inpatients with SpA in China, Xiao et al. found hematuria in 8.8%, proteinuria in 1.8%, a reduced estimated glomerular filtration rate (eGFR) in 0.3%, and nephrolithiasis in 13.0%. Nephrolithiasis was about twice as frequent as in matched controls from the general population (5.8%), and renal biopsy showed IgA nephropathy in 14 of 15 patients. The authors estimated eGFR with the simplified Modification of Diet in Renal Disease (MDRD) equation, which uses serum creatinine, age, sex, and race. They defined abnormal urinalysis as hematuria or proteinuria of at least 1+ on two consecutive tests and diagnosed nephrolithiasis by renal ultrasonography or a documented history of kidney stones [39]. In the international ASAS-COMOSPA study, 5.2% of patients had an eGFR below 60 mL/min/1.73 m². Renal impairment in that study was associated with older age, a negative HLA-B27 status, and higher C-reactive protein (CRP), but not with cumulative NSAID intake [40].

- *Hepatobiliary Involvement*

Patients with inflammatory arthritis develop nonalcoholic fatty liver disease (NAFLD) more often than the general population. Chronic inflammation, antirheumatic drugs, and metabolic comorbidities such as obesity, dyslipidemia, and metabolic syndrome contribute to this risk. In PsA, liver abnormalities affect about 30% of patients, and one study reported NAFLD in about 65% [41]. Comparable data for axial SpA are limited. Evaluation starts with liver enzymes (alanine and aspartate aminotransferase) and ultrasonography to detect hepatic steatosis. Liver biopsy remains the reference standard for assessing inflammation and fibrosis, but its invasiveness restricts it to selected cases [41].

Gallstone disease may also accompany chronic inflammatory arthritis, although data in SpA are scarce. In women with RA, García-Gómez et al. found gallstones in 33.3%, compared with 15.6% of population controls, and linked the excess to chronic inflammation and changes in high-density lipoprotein metabolism [42]. Ultrasonography is the first-line test, with a specificity of about 90% and the ability to detect stones as small as 2 mm. In acute cholecystitis, ultrasonography shows a gallbladder wall thicker than 3 mm, pericholecystic fluid, and tenderness over the right upper quadrant (sonographic Murphy sign). CT and MRI also visualize gallstones but are less sensitive for acute cholecystitis, and about 10% of gallstones contain enough calcium to appear on plain radiographs [43].

TABLE 1: Reported frequency of selected manifestations of spondyloarthritis in the reviewed studies.

Manifestation	Frequency	Setting and sample	Ref.
Inflammatory back pain	65%	Indonesia, single center (n = 40)	[7]
Radiographic sacroiliitis	70%	Indonesia, single center (n = 40)	[7]
Anterior chest wall pain	37.1%	France, single center (n = 275)	[23]
Peripheral arthritis	45%	Indonesia, single center (n = 40)	[7]
Peripheral joint disease, ever	57%	24 countries (n = 4,465)	[6]
Heel enthesitis	40%	Indonesia, single center (n = 40)	[7]
Enthesitis, ever	44%	24 countries (n = 4,465)	[6]
Dactylitis	7.5%	Indonesia, single center (n = 40)	[7]
Dactylitis, ever	15%	24 countries (n = 4,465)	[6]
Psoriasis	30%	Indonesia, single center (n = 40)	[7]
Acute anterior uveitis	2.5%	Indonesia, single center (n = 40)	[7]
Acute anterior uveitis	28%	France, single center (n = 275)	[23]
Hematuria	8.8%	China, single center (n = 350)	[39]
Nephrolithiasis	13.0%	China, single center (n = 350)	[39]
eGFR below 60 mL/min/1.73 m ²	5.2%	22 countries	[40]

Data from 24 countries come from ASAS-PerSpA, and data from 22 countries come from ASAS-COMOSPA, international cross-sectional studies of the Assessment of SpondyloArthritis International Society on peripheral involvement and on comorbidities in SpA, respectively. eGFR, estimated glomerular filtration rate.

Classification and Laboratory Evaluation

• ASAS Classification Criteria for Axial SpA

ASAS developed classification criteria for axial SpA in patients with back pain lasting at least three months and beginning before 45 years of age. A patient meets the criteria through one of two arms [2]:

- 1) Imaging arm: sacroiliitis on imaging plus at least one SpA feature. Sacroiliitis on imaging means active inflammation on MRI, such as bone marrow edema (osteitis) of the sacroiliac joints, or definite radiographic sacroiliitis according to the modified New York criteria (grade 2 or higher bilaterally, or grade 3 to 4 unilaterally).
- 2) Clinical arm: HLA-B27 positivity plus at least two other SpA features.

The SpA features are defined as follows [29]: inflammatory back pain; arthritis, meaning past or present active synovitis diagnosed by a physician; heel enthesitis, meaning past or present pain or tenderness at the insertion of the Achilles tendon or plantar fascia on the calcaneus; past or present anterior uveitis confirmed by an ophthalmologist; dactylitis diagnosed by a physician; psoriasis diagnosed by a physician; Crohn's disease or ulcerative colitis diagnosed by a physician; a good response to NSAIDs, meaning that back pain is gone or much better 24 to 48 hours after a full dose; a family history of SpA, meaning AS, psoriasis, uveitis, ReA, or IBD in a first- or second-degree relative; HLA-B27 positivity; and an elevated CRP.

In the validation cohort of 649 patients from 25 centers, the complete criteria set reached a

sensitivity of 82.9% and a specificity of 84.4%, and the imaging arm alone reached a sensitivity of 66.2% and a specificity of 97.3%. ASAS designed the criteria to classify patients for clinical studies; in practice, they can also guide clinicians who evaluate patients with chronic back pain [2].

• ASAS Classification Criteria for Peripheral SpA

ASAS uses a separate set of criteria for patients with peripheral-predominant disease. A patient with arthritis, enthesitis, or dactylitis meets these criteria when at least one of the following is present: uveitis, psoriasis, Crohn's disease or ulcerative colitis, a preceding infection, HLA-B27, or sacroiliitis on imaging. The criteria are also met when at least two of the following are present: arthritis, enthesitis, dactylitis, a history of inflammatory back pain, or a family history of SpA. In a cohort of 266 patients, these criteria had a sensitivity of 77.8% and a specificity of 82.9% [3].

• Laboratory Evaluation

A complete blood count (CBC) is a standard investigation in SpA because it reflects the systemic effects of inflammation. During active disease, chronic exposure to TNF- α and IL-6 induces hepatic production of hepcidin. Hepcidin blocks intestinal iron absorption and traps iron inside macrophages, which suppresses erythropoiesis in the bone marrow and results in anemia of chronic disease [44,45]. In patients with AS, this anemia improves after anti-TNF therapy [46]. Leukocyte and platelet counts tend to rise with disease activity. Active inflammation at the entheses mobilizes granulocytes

from the bone marrow into the circulation and produces mild to moderate leukocytosis, while IL-6 stimulates hepatic synthesis of thrombopoietin, which drives megakaryocytes in the bone marrow to overproduce platelets [44,45].

These cellular changes accompany a rise in acute-phase markers. CRP, an acute-phase protein produced by the liver in response to inflammation or infection, serves as a nonspecific marker of inflammatory activity. The erythrocyte sedimentation rate (ESR) increases as plasma fibrinogen rises and red blood cells settle faster [44,45]. Sustained elevation of CRP and ESR points to substantial systemic inflammation. A normal CRP does not exclude SpA, however: only 32.5% of the patients in the Surabaya cohort had an elevated CRP [7].

Assessment of Disease Activity

ASAS recommends the Ankylosing Spondylitis Disease Activity Score (ASDAS) to monitor disease activity and treatment response in axial SpA. The preferred version, ASDAS-CRP, combines four patient-reported items, each scored from 0 to 10 (back pain, duration of morning stiffness, peripheral pain or swelling, and the patient's global assessment of disease activity), with the serum CRP level in mg/L. The formula assigns a separate weight to each component, and CRP carries the largest coefficient [47]:

$$\text{ASDAS-CRP} = 0.12 \times \text{back pain} + 0.06 \times \text{duration of morning stiffness} + 0.11 \times \text{patient global assessment} + 0.07 \times \text{peripheral pain/swelling} + 0.58 \times \ln(\text{CRP} + 1)$$

Under the 2018 ASAS nomenclature, an ASDAS below 1.3 indicates inactive disease, 1.3 to less than 2.1 indicates low disease activity, 2.1 to 3.5 indicates high disease activity, and a score above 3.5 indicates very high disease activity. Earlier publications called the 1.3 to 2.1 band "moderate disease activity," so studies that use the older labels need careful comparison [48]. In the Surabaya cohort, 62.5% of patients had high disease activity by ASDAS-CRP, and serum IL-17 correlated with ASDAS-CRP ($r = 0.711$) [7].

CONCLUSION

SpA arises from the interplay of HLA-B27-related immune mechanisms, mechanical stress at the entheses, gut dysbiosis, and metabolic inflammation, which converge on the IL-23/IL-17 axis and TNF- α . The resulting inflammation of the entheses and bone marrow first causes bone loss and later new bone formation and ankylosis. The clinical spectrum extends from inflammatory back pain and sacroiliitis to anterior chest wall pain, asymmetric oligoarthritis of the lower limbs, dactylitis, enthesitis, uveitis, and involvement of the heart, lungs, kidneys, liver, and gallbladder. ASAS criteria offer a structured approach to classification, and ASDAS-CRP offers a validated measure for follow-up. Indonesian data remain limited to small single-center series; multicenter studies would clarify the local clinical pattern and help shorten the time to diagnosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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