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SPONDYLOARTHRITIS (M KHAN AND N AKKOC, SECTION EDITORS)

# Worldwide Differences in Clinical Phenotype of Axial Spondyloarthritis

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## Abstract

**Purpose of Review** This review aims to describe the variations in the clinical presentation of axial spondyloarthritis (axSpA) across the globe.

**Recent Findings** We searched the PubMed database and screened more than 1360 articles; 60 of them were selected based on relevance to the topic being discussed and the goals of the review. Most of the clinical manifestations, including IBP, peripheral arthritis, and extra-articular involvement are seen in different regions of the world, but with appreciable clinical heterogeneity, possibly related to a smaller number of patients from some countries, and global variation in the prevalence of HLA-B27. For example, HLA-B27-positive patients have an earlier age of onset, higher prevalence of acute anterior uveitis, and greater familial occurrence. Peripheral arthritis and enthesitis are most commonly seen among axSpA patients from Latin America and Asia, whereas IBD appears to be slightly more common among Middle Eastern and North African patients. The main weakness encountered while reviewing these data is that some studies were small, and others were cross-sectional and retrospective; hence the inferences may have a selection bias.

**Summary** AxSpA is a very heterogenous disease with varied presentation across the globe, in part related to HLA-B27 positivity. It is imperative to further investigate the key regional differences as they impact timely disease recognition and initiation of early treatment. Therefore, there is a need for a large worldwide systematic study to capture the clinical picture of AxSpA in a more uniform manner.

**Keywords** Axial spondyloarthritis · Ankylosing spondylitis · Clinical manifestations · HLA-B27 · Global review · Epidemiology

## Introduction

Axial spondyloarthritis (axSpA) is an inflammatory arthritis that primarily affects the sacroiliac joints and the spine (axial skeleton). Other musculoskeletal manifestations include root joint (hip and shoulder) arthritis, peripheral arthritis, enthesitis, and dactylitis. Additionally, patients may present with extra-musculoskeletal manifestations, such as acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis. AxSpA comprises the following two main entities: (1) the "classic" radiographic ankylosing spondylitis (AS) as defined by the modified New York criteria [1]. (2) The "spondylitic disease without radiographic evidence of sacroiliitis" [2], now renamed as "non-radiographic axial spondyloarthritis" (nr-axSpA), as defined by the 2009 ASAS classification criteria [3].

AxSpA is strongly associated with HLA-B27. There is a considerable variation in this association across the globe, with the strongest association seen in populations of European (especially northern Europe) and Asian descent, while it is almost absent in many regions of Sub-Saharan Africa [4–6]. The prevalence of axSpA is variable among different regions in the world and roughly correlates with the prevalence of HLA-B27. Dean et al. estimated the mean prevalence of AS (per 10,000) to be 31.9 in North America, 23.8 in Europe, 16.7 in Asia, 10.2 in Latin America, and 7.4 in Africa [7].

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## Methods

We searched the PubMed database using the terms: ankylosing spondylitis, axial spondyloarthritis, clinical variations/manifestations, Europe, Middle East, Africa, North America, Latin America, and Asia. There were 1360 articles screened and 60 were selected based on relevance to the topic being discussed and the goals of the review. Reasons for exclusion were articles discussing other rheumatic diseases, non-axSpA, and domains other than clinical manifestations such as genetics, pathogenesis, and imaging. We stratified patient populations according to the following 6 regions: Europe, Middle East, and North Africa (MENA), Sub-Saharan Africa, USA and Canada, Latin America including Mexico, and Asia.

### Europe

The earliest descriptions of AS originated in Europe [8]. Table 1 provides published data from cohorts in Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, the Netherlands, and the UK. Age at onset ranged between 20 and 35 years, and the diagnosis was delayed by 3 to 16 years. The most common clinical feature of AS/axSpA in this population has been inflammatory back pain (IBP), ranging between 80 and 100%. Among other features, peripheral arthritis (including root joints) ranged between 11 and 58% except in Greece where the prevalence was higher (72%) [9]. Enthesitis was present in 6% of Italians versus 71% of Swiss patients, and 4 to 13% had dactylitis [10, 11]. The percentage of positive family history, except for one Italian study, ranged between 35 and 46%. Acute anterior uveitis (AAU) was the most common extra-musculoskeletal manifestation being reported in up to 27% of Belgian patients; psoriasis ranged between 10 and 12% (except in the French cohort where it was 16%) and inflammatory bowel disease (IBD) between 5 and 12% (except in Greece where no cases were reported) [9, 12, 13]. HLA-B27-positive patients have a younger age at disease onset and shorter delay in diagnosis as compared to HLA-B27 negative patients [14, 15].

### The Middle East and North Africa

There are a good number of articles originating from the Middle East and North Africa (MENA) regarding the clinical features of AS. Table 2 lists the data from Algeria, Egypt, Iran, Saudi Arabia (KSA), Kuwait, Lebanon, Morocco, Tunisia, Turkey, and the United Arab Emirates (UAE). We have combined data from the three neighboring countries (KSA, Kuwait and UAE) as each country reported less than 18 patients [22–24). Most of these studies included only AS patients, except the ones from Lebanon and Tunisia that also included patients with nr-axSpA [25, 26], most (55–84%) were males, and 72–84% presented with IBP (except for Iran 44% and Egypt 49%) [27, 28]. HLA B27 association was weaker than reported from Europe. Duration of symptoms before diagnosis was longer in the North African compared to the Middle Eastern patient population (10–15 years vs 6–9 years, respectively), which could reflect accessibility to healthcare. Disease activity scores were not consistently reported.

Family history of SpA was reported in 6 studies, and it ranged between 9 and 29%. Kuwait was the only country that reported positive family history in more than 30% of the patients, but the sample size was only 17 patients [23]. The occurrence of peripheral arthritis averaged around 36%. Hip involvement was more frequent in North Africa (up to 47% in patients from Morocco) compared to 25% in Lebanon and Kuwait [23, 26, 29]. Enthesitis varied widely between different studies, 22% in Tunisia vs 92% in Turkey [25, 30]. The prevalence of dactylitis was only 1.5–2%. AAU was less common compared to European cohorts, but it occurred in up to 45% of the Iranian patients [28]. IBD and psoriasis, reported only in Lebanon and Tunisia, were higher than among European cohorts [25, 26, 31]. An older publication based on a cohort of 518 north-African patients (from Tunisia, Algeria, and Morocco) with spondyloarthritis (SpA) according to Amor criteria, had a mean age at diagnosis of 26.6 years, the male-to-female ratio of 3:1, and IBP prevalence of 90% [32]. Sacroiliitis was reported by 97% of the patients, peripheral arthritis (including root joints) by 42%, and dactylitis by 10%.

### Sub-Saharan Africa

Data on axSpA in Sub-Saharan Africa has been very scarce, based on articles from Burkina Faso, the Democratic Republic of the Congo (DRC), Togo, Zimbabwe, and South Africa. They discussed AS, and only one paper from DRC included nr-axSpA patients [34]. The recognition of nr-axSpA can be very challenging as the ASAS criteria might not be applicable because of the very low prevalence of HLA B27 and the lack of access to magnetic resonance imaging (MRI). Lebughe et al. [34] analyzed data from 59 patients with axSpA; 56% were males, mean age of onset was 38 (±4.5) years, 86% had inflammatory back pains, 72% had buttock pain, 31% had peripheral arthritis, and 22% had enthesitis. No patients had hip involvement. AAU and psoriasis were reported in 15% and 2% of the cases, respectively. Although commonly reported in North Africans, familial occurrence has rarely been documented in South Africa. Mijiyawa et al. reported similar findings based on 26 patients (92% males) from South Africa, Zimbabwe, and Togo, only one patient

**Table 1** Differences in disease phenotype in European patients with AS/axSpA

| Countries | Belgium | | France | Germany | | Greece | Italy | Portugal | Spain | Sweden | Swiss | Netherlands | UK |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cited studies | Varkas [12] | | Costantino [13] | Rudwaleit [16] | | Kassimos [9] | Bandin [10] | Pimentel-Santos [17] | Collantes [18] | Exarchou [19] | Neuensch [11] | DeJong [20] | Der. [21] |
| # Patients | 847 | 679 | 462 | 285 | 135 | 369 | 842 | 11,030 | 477 | | | 313 | 2420 |
| Type | AS | Nr-axSpA | axSpA | AS | Nr-axSpA | AS | AS | AS | AS | AS | Nr-axSpA | axSpA | axSpA |
| Males % | 68 | 49 | 45.5 | 64 | 43 | 100 | 67 | 63 | 76 | | 48 | 58 | 68 |
| Mean age at onset | 28 | 33 | 21 | 30 | 33 | 20 | | 27 | 26 | | 28 | 35 | |
| HLA B27+ | 83 | 76 | 58 | 82 | 75 | 90 | 83 | 81 | 84 | | 71 | 58 | 80 |
| Delayed diagnosis (years) | 16 | 6 | | 5 | 3 | 5.3 | | 11 | 14 | | 9 | 4 | 16 |
| BASDAI | 5.5 | 4.8 | 4.48 | 4 | 4 | | | 4.2 | | | 4.9 | 4.8 | |
| BASFI | 5.2 | 3.4 | 3.06 | 3 | 2.5 | | | 4.1 | | | 3 | | |
| BASMI | | | 2.19 | 2 | 1.1 | | | 4.0 | | | 1.3 | | |
| +FHx % | 46 | 39 | | 37 | 35 | | 8 | | | | 36 | 36 | |
| IBP % | | | | 99 | 100 | 100 | 87 | 83 | 96 | | 79 | 91 | |
| Arthritis %* | 57 | 55 | 57.6 | 37 | 41 | 72 | 21 | 43 | 11 | 18 | 37 | 42 | |
| Enthesitis % | | 48.6 | 39 | 44 | | 6 | 7 | 25 | | 71 | 40 | | |
| Dactylitis % | | 13.4 | 6 | 4 | | | | | | 11 | 5 | | |
| AAU % | 27 | 17 | 8.5 | 21 | 12 | 11 | 1.5 | | 22 | 24 | 16 | 22 | 23 |
| IBD % | 10 | 6 | 5 | 2.6 | 1.8 | 0 | | | | 8 | 7 | 12 | 10 |
| Psoriasis% | 11 | 11 | 16.2 | 10 | 10 | | | | | 7 | 9.1 | 12 | 11 |

The asterisk (*) indicates that "Arthritis %" includes involvement of root joints (hip and/or shoulder)

*BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *+FHx*-positive family history, *IBP* inflammatory back pain, *AAU* acute anterior uveitis, *IBD* inflammatory bowel disease

**Table 2** Disease phenotype in patients with AS/axSpA from the Middle East and North Africa

| Countries | Algeria | Egypt | Iran | KSA Kuwait UAE | Lebanon | Morocco | Tunisia | Turkey |
|---|---|---|---|---|---|---|---|---|
| Cited studies | Haid [33] | Tayel [27] | Nazarinia [28] | Al-Arfaj [22] Uppal [23] Al-Attia [24] | Ziade [26] | El Mansouri [29] | Ben-Abdel-ghani [25] | Karaarslan [30] |
| # Patients | 325 | 34 | 98 | 49 | 141 | 117 | 200 | 339 |
| Type | axSpA | AS | AS | AS | axSpA | AS | axSpA | AS |
| Males % | | 84 | 71.4 | 67–82 | 61.7 | | 69 | 55 |
| Mean age at onset | | | | 23–28 | | 25 | | |
| HLA B27 + | | 58.6 | 73.4 | 67 | 41.1 | | 51 | 61 |
| Delay in diagnosis (years) | | | | | 6.6 | 10.4 | 15 | 9 |
| BASDAI | 5.6 | 4.16 | | | 3.6 | 3.3 | | 5 |
| BASFI | | 5.12 | | | | 3.9 | | 3.7 |
| + FHx % | | | 14.3 | 13–34 | 29.1 | 12 | 9 | |
| IBP % | 73 | 49 | 44.2 | 72–73 | 81 | 84 | | |
| Arthritis % | | 38 | 30 | 24–65 | 37 | 36 | 42 | 33 |
| Hip invol | | | | 12–25 | 25 | 47 | | |
| Enthesitis % | | | 35 | 25–60 | 30 | 12 | 22 | 92 |
| Dactylitis % | | | | | 2.1 | | 1.5 | |
| AAU % | 20 | | 45 | 7–20 | 8.5 | 7 | 17 | 18 |
| IBD % | | | | | 18.4 | | 14.5 | |
| Psoriasis% | | | | | 19.1 | | 4.5 | |

had positive HLA B27 (4%) [5]. It is already well described in other populations that HLA-B27 negative patients with AS have a later age of onset, and lower prevalence of AAU and familial occurrence [5]. Ouedraogo et al. reported 13 patients with AS, most of them were males, and none of them had extra-articular manifestations [35]. It is of interest to mention that in some countries in West Africa, e.g., among the Fula ethnic group in Gambia, AS prevalence is virtually absent despite a 6% HLA-B27 positivity rate in the general population [36].

## North America (USA and Canada)

USA and Canada have one of the most ethnically diverse populations in the world, and there is a need for proper nationwide studies comparing the various clinical features of axSpA in these countries. Mease et al. analyzed 407 patients from the US-based Corrona registry, 310 had AS and 97 had nr-axSpA, 64% were males, 88% were White, 2.8% were Asians and 1.5% were Black [37]. The mean disease duration was 10.4 years ± 11.3. HLA-B27 test was positive in 71% among those who had the test done. The mean disease activity scores revealed moderate disease activity, enthesitis was present in 33% and dactylitis in 10% of the patients. Family history of SpA was positive in 14%. AAU was the most common extra-articular manifestation at 17%, psoriasis at 10%, and IBD at 7%. Khan et al. [38] had reported clinical features and HLA-B27 prevalence among African American and white patients with AS. African American patients had later age of onset, lower incidence of AAU, and a weaker association with HLA-B27. The native tribes in North America have mostly been studied with regards to their association with HLA-B27. Inuits and Eskimos in Alaska and Northern Canada, as well as the Navajo tribes in the USA, tend to have a greater incidence of reactive arthritis than AS, in contrast to Haida people living in Canada who suffer predominantly from AS [39]. Psoriasis and IBD were very rare among these populations that are ethnically unmixed with whites.

A study by Singh et al. [40] evaluated the racial differences in clinical features from an American database that included 10,990 patients with AS. Male to female ratio was 1:1, and 8% of the participants were African Americans. Peripheral arthritis was present in 73%, enthesitis in 25%, and dactylitis in only 5%. Psoriasis occurred in 10% of the cases, and was less common among African Americans.

## South America

Table 3 lists the differences among clinical phenotypes in patients from Latin countries in South America. Most of the studies described axSpA as part of the bigger family of SpA which includes PsA among other conditions, and this makes sample sizes of AS patients much smaller

**Table 3** Differences in disease phenotype in patients with AS from Latin countries of South America

| Countries | Argentina | Brazil | | Chile | Colombia | Peru | Uruguay | Venezuela |
|---|---|---|---|---|---|---|---|---|
| Study | Buschiazzo [43] | S-B [41] | S-B [44] | Gutierrez [45] | V–O [42] | C–C [46] | Palleiro [47] | Chacon [48] |
| # Patients | 86 | 147 | 736 | 64 | 55 | 32 | 28 | 38 |
| Type | AS | AS | AS | AS | AS | AS | AS | AS |
| Males % | 88 | 84 | 77 | | | | | |
| Mean age at onset | | | 28 | | 27 | | 32 | |
| HLA B27 + | | 78 | | | 60 | | | |
| Delayed diagnosis (years) | 9.5 | | | 8.5 | | | | |
| + FHx % | 21 | 14 | 17 | | 18 | | | 27 |
| IBP % | | 62 | 74 | 74 | | | 41 | 74 |
| Arthritis % | | 22 | 38 | 59 | | 43 | 41 | 51 |
| Hip invol.% | | 36 | 31 | | | | | |
| Enthesitis % | | 22 | 23 | | | | 28 | 35 |
| Dactylitis % | | | 5 | | | 30 | | |
| AAU % | | 14 | | 18.6 | 7.2 | | | 22 |

when compared with other regions of the world. Brazil is an exception where axSpA was studied more extensively, and all their axSpA patients had AS. Patients were predominantly males (77–88%), and their age at diagnosis was 27 to 32 years. HLA B27 positivity was reported in two studies and it ranged between 60 and 78% [41, 42]. Surprisingly, inflammatory back pain was less common (41–74%), while a good percentage of the patients presented with peripheral arthritis (22–59%) and enthesitis (22–35%). The prevalence of AAU was 7–22%. No data on IBD and psoriasis in axSpA were available. Sampaio-Barros et al. [41] reported that African-Brazilians patients with AS had a lower prevalence of HLA B27 (69%) as compared to Brazilian AS patients of European descent (81%), and less familial occurrence (2.8% vs 18%), confirming similar finding noted in Sub-Saharan African and African-American patients [38]. The African-Brazilians had less thoracic/cervical involvement compared to Caucasian Brazilian patients with AS (58 vs 74%), and more hip involvement (42 vs 24%).

## Central America and Mexico

There are only a few articles from Central America that targeted clinical manifestations of axSpA [49]. A 1989 study described the pattern of AS in the Mexican Mestizo (native Americans with variable level of Spanish genetic admixture) population [50]. It included 87 patients, 46% of whom had juvenile-onset. 50.6% of the patients presented with spinal involvement, 65.5% with peripheral arthritis, and 47.1% with enthesopathy. There was a difference in presentation between children and adults, with adults having more spinal involvement (82.5% vs 23.4%). Uveitis prevalence was estimated at 20.6%. One of the debilitating symptoms in SpA is midfoot arthritis (tarsitis); this has been especially described in Mexican patients [51, 52]. An article from 1984 estimated the prevalence of HLA-B27 positivity among Mexican Mestizo AS patients to range between 68.6% and 80.77% [53]. Subsequent studies from Mexico were either purely prevalence studies or compiled all SpA conditions in their analysis, which makes it difficult to make conclusions regarding clinical manifestations of AxSpA. Similarly, studies from Costa Rica, El Salvador, and Guatemala did not specifically target the clinical manifestations of axSpA [54].

## Asia

We reviewed data that originated from China, India, Nepal, Bangladesh, Pakistan, Hong Kong, Taiwan, South Korea, Japan, Thailand, and Singapore (Table 4). We did not include publications from Australia and New Zealand under this section because the clinical findings of axSpA are very similar to those from Europe. A cross-sectional observational study of axSpA patients encompassed 4131 Chinese patients; 89.4% of them were HLA-B27-positive, 73% were males, the mean age of onset was 26 years, and family history was positive in ~ 23% of the cases [55]. Peripheral arthritis and hip involvement were estimated at 35% and 30%, respectively. Enthesitis was predominant with ~ 65% of patients affected. AAU was the most common EAM with a prevalence of ~ 10%. The presence of HLA-B27 was associated with younger age, male sex, a longer disease duration (more than 3 years), a higher frequency of uveitis, and greater family aggregation [55]. On the other hand, the absence of HLA-B27 was associated with longer delay in diagnosis (> 36 months) and higher frequency of psoriasis.

Two studies from Taiwan had very similar results to China where the majority of AS patients had positive HLA-B27 (92%); around 49% had peripheral arthritis and 27%

**Table 4** Differences in disease phenotype in patients with AS/axSpA from Asia

| | China | | India | | Hong Kong | | | Taiwan | | Korea | | | Japan | Thailand | Singapore | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Zhang [55] | Lin [72] | Agg. [61] | Pra. [62] | Tsang [58] | Chung [59] | Au [60] | Wong [56] | Huang [57] | Baek [66] | Jeong [65] | | Kishimoto [67] | Chiowcha [68] | Hong [69] | |
| # Patients | 4131 | 455 | 70 | 51 | 153 | 92 | 165 | 362 | 391 | 67 | 459 | 155 | 77 | 88 | 215 | 47 |
| Type | axSpA | axSpA | AS | AS | axSpA | AS | AS | AS | AS | AS | AS | Nr-axSpA | axSpA | AS | AS | Nr-axSpA |
| %Males | 73 | 68 | 84 | 94 | 57 | 73 | 74.5 | 69 | 70 | 89.6 | 83 | 66 | 74 | 65 | 81 | 70 |
| Mean age at onset | 27 | | 24 | 21 | | | | 30 | 30 | 22 | 25.9 | 29.5 | 24.2 | 28.8 | 31.8 | 31 |
| %HLA B27+ | 89 | 72 | 93 | 94 | 79 | | 96 | 92 | 93 | 98.5 | 93 | 96 | 79.6 | 89.7 | 82 | 68 |
| Disease duration | 6.69 | 2.62 | 9.3 | 8.7 | 10.8 | 18.7 | 11 | 11.8 | 11.4 | 10.8 | 6.5 | 1.7 | | 11.7 | 14.8 | 8.9 |
| BASDAI | 3.68 | | 3.2 | | 4.4 | 4.1 | 3.93 | 4.1 | 4.1 | | | | 2.8 | | 3.5 | 4.2 |
| BASFI | | | 2.3 | | 2.9 | 3.2 | 1.8 | 2.3 | 2.3 | | | | 1.6 | | 2.1 | 2.1 |
| +FHx % | 23 | 26 | 53 | 12 | 27.5 | | | 44 | | | | | | 32 | 15 | 13 |
| IBP % | | 67 | 87 | | 68 | | | | | | | | 96 | 85 | | |
| Arthritis% | 35 | 37 | 66 | 61 | 52 | 45 | 42 | 48 | 49 | 58 | 24 | 39 | 62 | 75 | 47 | 51 |
| Enthesitis% | 65 | 53 | 63 | | 44 | 7.6 | 30 | | | 82 | 9.6 | 19.4 | 52 | 57 | 33 | 30 |
| Dactylitis% | 6.2 | 1.8 | | | 9.2 | 13 | 6.7 | | | | | | 15.6 | 11.4 | 7 | 2 |
| AAU % | 10.5 | 9 | 25.7 | 22 | 25 | 49 | 7.3 | 27.1 | 27.4 | 28.4 | 20.5 | 23.9 | 27.3 | 28.4 | 33 | 17 |
| IBD % | 1.6 | 0.2 | | | 2 | | | 5 | 4.6 | | 0.4 | 0.6 | 7.8 | 1.1 | | |
| Psoriasis% | 0.9 | 0.4 | | | 17.6 | | | 13 | 13 | | 1.1 | 0.6 | 16.9 | 0 | 5 | 4 |

had AAU [56, 57]. Psoriasis was reported in 13% of the participants with AS, while ~ 5% had IBD symptoms. Three studies from Hong Kong included patients with AS and nr-axSpA [58–60], one of them reported a prevalence of AAU up to 49% in AS patients, and the study that included nr-axSpA patients had more female participants (43%) and lower rates of HLA-B27 positivity (79%). The disease in China and Taiwan often has juvenile onset with peripheral arthritis or enthesitis.

The data from South Asia are sparse. There are 3 studies from India and one study from Bangladesh, Nepal, and Pakistan each [61–64]. Different studies from South Asia have revealed IBP pain being the main symptom in patients with AS; it was reported in 100% of patients in India but only 40% of patients in Nepal and Bangladesh. Peripheral arthritis was seen in 60% of patients in India which is higher than in the rest of the world. The reason could be that the patient included in the study may have had reactive arthritis and the poor socioeconomic status of the country might have contributed to it. The disease, as in China and Taiwan, often has juvenile-onset with peripheral arthritis or enthesitis. The frequency of uveitis was variable with one small study revealing it to be as high as 25% [61]. Enthesitis has also been a predominant feature reported between 55 and 68% of patients in Nepal and Bangladesh [63]. One small study from Pakistan included 32 patients with AS and found that the mean age of disease onset was 26.1 years. 84% were HLA-B27-positive; 93% presented with axial joint involvement while 6% presented with peripheral arthritis [64].

One retrospective analysis from South Korea examined 155 nr-axSpA and 459 AS patients; another study examined 67 patients with adult onset AS [65, 66]. Spinal symptoms were the presenting manifestation in 80% of the patients. 24–58% had hip, shoulder, and peripheral joint involvement. The knees and ankles were the most commonly affected peripheral joints, with asymmetric and oligoarticular distribution. The prevalence of enthesitis varied significantly among the two studies; it ranged from 9.6 to 82.1%. The prevalence of AAU ranged between 20 and 28%, while that of IBD and psoriasis was very low, less than 1%.

A Japanese study using the ASAS-COMOSPA (Assessment of Spondyloarthritis international Society–COMOrbidities in SPondyloArthritis) data included a total of 3984 patients [67]. This study compared 161 Japanese patients, 933 patients from other Asian countries (China, Singapore, South Korea, Taiwan), and 2890 patients from other regions of the world (Europe, the Americas, Africa). Most Japanese patients had IBP as a presenting symptom (96%) with ~ 80% having HLA-B27 positivity. More than half of the participants had peripheral arthritis and enthesitis (62 and 52% respectively). The prevalence of dactylitis was higher in Japanese patients (16%). Psoriasis and IBD (17 and 8% respectively) were more prevalent in the Japanese population compared to other Asian countries.

One study from Thailand enrolled 88 AS patients, 35% of whom were females [68]. IBP, peripheral arthritis, and enthesitis were very prevalent, psoriasis was absent, but AAU was reported in up to 29% of the patients. A Singapore multi-ethnic Asian cohort, using data from the PREcision

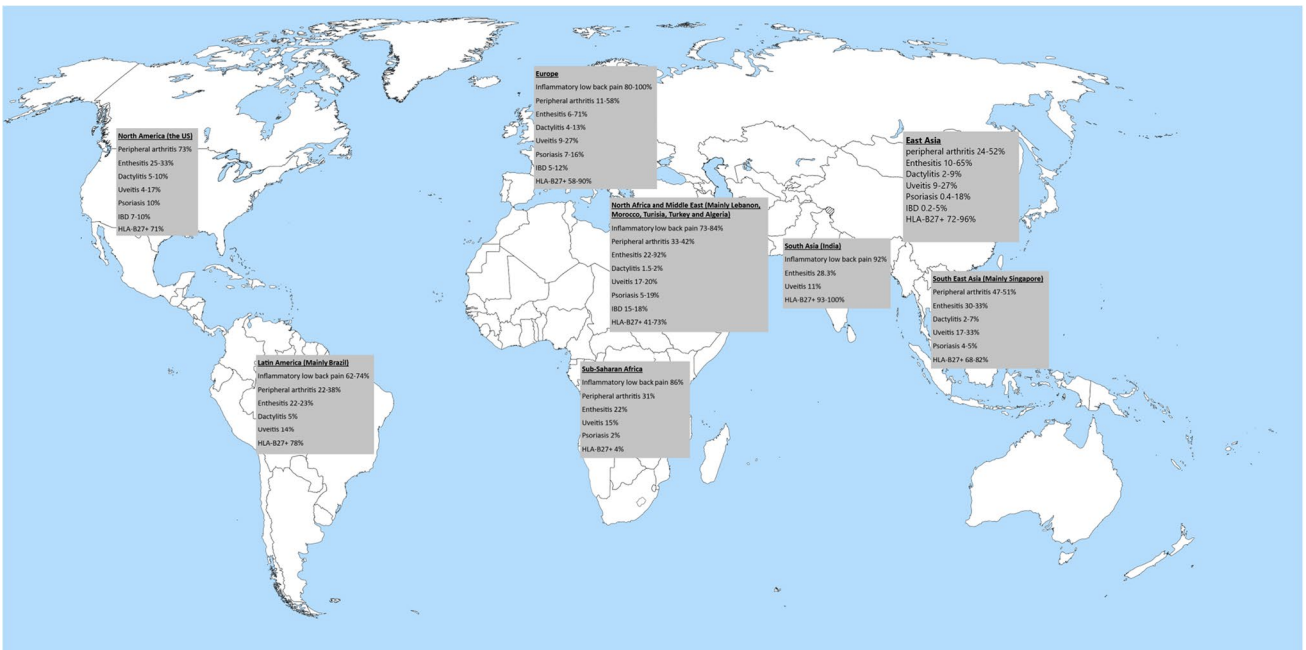


**Fig. 1** Summary of the clinical manifestations of axSpA in different regions of the world

medicine in SPONdyloarthritis for Better Outcomes and Disease Remission (PRESPOND) registry, included 262 axSpA patients (82% Chinese, 79% male) to compare the differences between patients with AS and nr-axSpA [69]. The mean age (SD) at diagnosis was 32.4 (13.1) years, which was similar between AS and nr-axSpA patients. Patients with AS were more likely to be HLA-B27-positive, have AAU, and have worse spinal mobility. These patients were also older (mean age 42.7 vs 37.4 years for nr-axSpA) and had a longer disease duration (10.9 vs 6.4 years, respectively). Peripheral arthritis was present in almost half of the subjects, with ~ 30% having enthesitis and AAU symptoms. The prevalence of AS is much higher in Chinese-Indonesians compared to the native population that mostly possess the HLA-B*27 subtype that virtually lacks any association with AS [70]. Despite this difference, the clinical features were very similar in a study of 72 patients with SpA [71].

## Conclusion

This review has summarized the clinical presentations of AS/AxSpA across the globe (Fig. 1). It is well recognized that there is a considerable variation in the reported prevalence of AxSpA. Most of the clinical manifestations, including IBP, peripheral arthritis, and extra-articular involvement are seen in different regions of the world, but with appreciable clinical heterogeneity, possibly related to a smaller number of patients from some countries, and global variation in the prevalence of HLA-B27. For example, HLA-B27-positive patients have an earlier age of onset, higher prevalence of acute anterior uveitis, and greater familial occurrence. Peripheral arthritis and enthesitis are most commonly seen among axSpA patients from Latin America and Asia, whereas IBD appears to be slightly more common among Middle Eastern and North African patients. The main weakness encountered while reviewing these data is that some studies were small, and others were cross-sectional and retrospective; hence, the inferences may have a selection bias. There is a need for a large systematic worldwide study to capture the symptomatology of AxSpA in a more uniform pattern. It is imperative to further investigate the key regional differences as they impact on timely disease recognition and initiation of early treatment.

## Declarations

**Ethics Approval and Consent to Participate** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Competing Interests** Mohamad Bittar declares that he has no competing interests.

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