Raising the bar for classification and outcome assessment for clinical studies in axial spondyloarthritis

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CHAPTER 3

AGE AT ONSET IN AXIAL SPONDYLOARTHRITIS AROUND THE WORLD: DATA FROM THE ASSESSMENT IN SPONDYLOARTHRITIS INTERNATIONAL SOCIETY PERIPHERAL INVOLVEMENT IN SPONDYLOARTHRITIS STUDY

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ABSTRACT

Background

Age at onset is useful in identifying chronic back patients at an increased risk of axial SpA (axSpA). However, the majority of data on which the criterion of age at onset <45 years is based originates from Europe. Therefore it is unknown if this criterion applies in other parts of the world. We aimed to assess age at onset of axSpA and its relationship with HLA-B27 and gender across the world.

Methods

Analyses were applied to patients from 24 countries across the world with an axSpA diagnosis and known age at onset of axial complaints. Cumulative probability plots were used to display the cumulative distribution of age at onset of axial symptoms. Linear regression models were built to assess the effect of HLA-B27 and gender on age at onset of axial symptoms.

Results

Of 2579 axSpA patients, 92% had an age at onset of axial symptoms <45 years, with only small variations across the geographical regions [Asia, n=574 (94%); Europe and North America, n=988 (92%); Latin America, n=246 (89%); Middle East and North Africa, n=771 (91%)]. Age at onset of axial symptoms was consistently lower in HLA-B27-positive patients {median 25 years [interquartile range (IQR) 19–32] vs 31 [IQR 22–39]} and male patients [median 25 years (IQR 19–33) vs 28 (IQR 21–37)], but in multivariable models an additional statistically significant effect of male gender independent of HLA-B27 was only found in Asia.

Conclusion

Around the world, the great majority of axSpA patients had an age at onset of axial disease of <45 years, with HLA-B27 and male gender associated with earlier disease onset.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic, inflammatory disease predominantly affecting the sacroiliac joints and spine. HLA-B27 is the most important genetic risk factor for axSpA and has been reported to be associated with earlier onset of disease[1-4]. Data regarding the association between gender and age at onset of disease are ambiguous[5], even though there is a known difference in disease severity and disease expression between male and female patients[2, 4, 6].

AxSpA usually starts in the second or third decade of life[7, 8]. Age at onset of axSpA after 50 years appears to be uncommon[9], thus age at onset can be very useful in identifying chronic back pain patients suspected of axSpA[2], as it is an easy and accessible piece of information that can be used in the first selection of patients.

Previous research has shown that the vast majority of axSpA patients develop back pain before the age of 45 years[1, 10, 11], which formed the basis for the Assessment of Spondyloarthritis international Society (ASAS) definition of inflammatory back pain (IBP)[12] and the prominent place of age at onset in the current ASAS classification criteria for axSpA[13]. In fact, the criterion of onset before the age of 45 is an important difference between the modified New York (mNY) criteria for classification of AS[14] and the ASAS classification criteria and is even the main cause for discrepancy between the two criteria sets in classifying patients with radiographic axSpA (r-axSpA)[15]. Since the publication of the ASAS criteria for axSpA, some data have become available on the age at onset of axSpA patients in Brazil[3 16] and China[17], but the majority of the data originates from Western Europe.

Given that both prevalence of axSpA[18] and its main genetic risk factor HLA-B27[19] vary considerably throughout the world, a similar distribution in age at onset to the patients in the Feldtkeller study[1] in other parts of the world is not a given. Then again, since age at onset plays an important role in diagnosing patients with axSpA as well as in the classification of patients, the age at onset criterion should be representative of patients all around the world. Hence, the aim of this study was to assess age at onset of axSpA as well as its relationship with HLA-B27 and gender in various regions of the world, using data from the Assessment in SpondyloArthritis international Society peripheral involvement in Spondyloarthritis (ASAS-PerSpA) study[20].

MATERIALS AND METHODS

This study was conducted using data from the ASAS-PerSpA dataset, which has been described elsewhere[20]. In brief, ASAS-PerSpA was a multicentre observational study with a cross-sectional design, in which a total of 24 countries participated. Its main aim was to investigate clinical peripheral rheumatologic features in consecutively included SpA patients and evaluate the validity of existing outcome measures of peripheral rheumatological features.

Patients

In the ASAS-PerSpA study, patients with a diagnosis of spondyloarthritis (n=4465) were included between July 2018 and February 2020, representing 24 countries in four geographical regions. The study was approved by the ethical committees in all countries (complete list available in Supplementary Data S1, available at Rheumatology online), and written informed consent was obtained from participants prior to inclusion. For this analysis, only patients with a definite diagnosis of axSpA were included, which was defined as axSpA and either r-axSpA or non-radiographic axSpA (nr-axSpA) as a disease subgroup.

Outcomes

The primary outcome of interest was the age at onset of axial symptoms across all patients with a diagnosis of axSpA and stratified by geographical region. Age at onset was ascertained from the date of first axial symptoms, as reported by the rheumatologist, and the study date. Negative values for age at onset of axial symptoms were recoded to missing values (n=3).

Additional outcomes of interest were the association between HLA-B27 and age at onset of axial symptoms and the association between gender and age at onset of axial symptoms in the total included axSpA population and each of the geographical regions.

Analyses

Analyses were restricted to patients with a known age at onset of axial complaints. Categorical variables were reported as frequencies (proportions) and continuous variables as mean and S.D. in case of normally distributed data and as median and interquartile range (IQR) in case of non-normally distributed data.

Cumulative probability plots were used to display the cumulative distribution in age at onset of axial symptoms. Mann–Whitney U tests were used to compare the median age at onset of axial symptoms between groups stratified for HLA-B27 status or gender.

Linear regression models were built to assess the association between HLA-B27 status or gender and age at onset of axial symptoms with HLA-B27 status or gender as the independent variable and age at onset as a dependent variable. Finally, a multivariable linear regression model including both HLA-B27 status and gender as covariates was built to assess whether the association between HLA-B27 and age at onset was different for male and female patients.

Data were analysed using Stata SE version 16 (StataCorp, College Station, TX, USA). P-values <0.05 were considered statistically significant.

RESULTS

A total of 2579 patients had a definite diagnosis of axSpA and a known age at onset of axial complaints. Patients were grouped in four previously defined geographical regions: Asia (n=574), Europe and North America (n=988), Latin America (n=246) and the Middle East and North Africa (n=771) (Supplementary Table S1, available at Rheumatology online). Overall there was only a small percentage of missing data (<5% unless indicated otherwise), with the exception of HLA-B27 status and MRI of the pelvis, where information was unavailable for a larger proportion of patients, which was especially apparent in the Middle East and North Africa population.

Across the board, 69% of included patients were male, 79% were HLA-B27 positive, the vast majority (94%) had IBP according to the ASAS definition[21], the majority (78%) had r-axSpA and the level of confidence regarding the diagnosis axSpA was high, with very small variations between geographical regions (Table 1). Asian patients had a somewhat lower median age and shorter median symptom duration. Latin American patients more frequently had peripheral symptoms, as shown by the higher percentages of peripheral arthritis, enthesitis and dactylitis; uveitis was also more common compared with patients from the other geographical regions. Noticeably, biological DMARD use was much higher in Latin America compared with the other regions.

Table 1 Characteristics of the axSpA patients from the ASAS-PerSpA study analysed in this study, stratified by geographical region

	Total *n=2,579*	**Asia** *n=574*	**Europe & North America** *n=988*	**Latin America** *n=246*	**Middle East & North Africa** *n=771*
Gender, male	69%	79%	65%	70%	65%
Age, median (IQR)	40 (31-51)	34 (27-45)	44 (35-53)	42 (34-53)	39 (32-49)
Symptom duration (yrs), median (IQR)	11 (5-19)	8 (4-15)	13 (7-24)	12 (5-20)	10 (5-16)
HLA-B27 positive	79%**	89%*	79%**	81%**	67%***
IBP ASAS definition[†]	94%	91%	95%	96%	95%
Positive family history	34%	30%	38%	27%	36%
Peripheral arthritis	44%	52%	38%	72%	36%
Enthesitis	45%	53%	37%	71%	42%
Dactylitis	6%	7%	5%	16%	3%
Psoriasis	8%	4%	13%	4%	5%
IBD	5%	1%	7%	4%	6%
Acute anterior uveitis	22%	24%	25%	31%	15%
Elevated CRP	70%	74%	66%	77%	70%
Sacroiliitis on radiographs[‡]	78%	85%	73%	75%*	79%
Sacroiliitis on MRI[‡]	82%***	78%***	77%***	81%***	93%***
Number of SpA features[§], mean (SD)	4 (2)	4 (1)	4 (2)	4 (2)	3 (2)
Use of bDMARD	33%*	39%**	25%	58%	31%*
Use of NSAID	99%*	99%**	99%	99%	98%*
LoC regarding axSpA, mean (SD)	8 (3)	7 (3)	8 (3)	7 (4)	9 (2)

[†] 4 out of 5 of the following features: onset before the age of 40, insidious onset, improvement with exercise, no improvement with rest, pain at night[21]. [‡] Based on reading of local radiologists. [§] Excluding HLA-B27 status and sacroiliitis on imaging. * 5-10% missing values, ** 10-20% missing values, ***20-40% missing values **ASAS**, Assessment of SpondyloArthritis international Society; **axSpA**, axial spondyloarthritis; **bDMARD**, biological Disease Modifying Anti-Rheumatic Drug; **CRP**, C-reactive protein; **HLA-B27**, Human Leucocyte Antigen B27; **IBD**, Inflammatory Bowel Disease; **IBP**, Inflammatory Back Pain; **IQR**, interquartile range; **LoC**, Level of Confidence regarding the diagnosis; **MRI**, Magnetic Resonance Imaging; **NSAIDs**, Non-Steroidal Anti Inflammatory Drugs; **SpA**, Spondyloarthritis.

Age at onset of axial symptoms

The median age at onset of axial symptoms in all included patients with axSpA was 26 years (IQR 20–34), with the lowest age at onset in Asia [24 (19–31)] followed by Europe and North America [26 (20–35)], Latin America [27 (21–40)] and Middle East and North Africa [27 (21–35)] (Fig. 1). The majority (92%) of patients with axSpA had an age at onset of axial symptoms <45 years, with only a small variation across the various geographical regions (Fig. 1). This finding was even more pronounced in the HLA-B27-positive subgroup (Fig. 1 and Supplementary Table S2, available at Rheumatology online) in which 94% of patients had an age at onset of axial symptoms <45 years. Additionally, only in a very small proportion (4%) of patients did the axial complaints start after the age of 50 years. Cumulative distribution plots showed that among all axSpA patients, 95% developed axial complaints before the age of 48 years and this was before the age of 46, 47, 51 and 48 years for the Asian, European and North American, Latin American and Middle Eastern and North African populations respectively (Fig. 1). Patients with an onset of axial complaints

at the age of ≥45 years were less often male, had a shorter median symptom duration, were less often HLA-B27 positive and had IBP less often compared with patients with an age at onset <45 years (Table 2). Elevated CRP and sacroiliitis on radiographs were also less frequent in patients with an age at onset ≥45 years.

Association between gender and age at onset

In the total included axSpA population, the median age at onset of axial symptoms of male patients [25 years (IQR 19–33)] was significantly lower than that of female patients [28 years (IQR 21–37)] (P<0.001). This difference was seen in Asia [23 years (IQR 19–31) vs 28 (21–37), P=0.015], Latin America [26 (19–34) vs 34 (22–43), P¼0.002] and the Middle East and North Africa [26 (20–33) vs 29 (23–37), P<0.001], but was less pronounced in Europe and North America [26 (20–34) vs 28 (20–36), P=0.053] (Fig. 2). Linear regression models showed a significant effect of gender on the age at onset of axial symptoms in the total study population (P<0.001) and the Asian (P=0.010), Latin American (P=0.001) and Middle Eastern and North African (P<0.001) populations, but just missed the significance level in the European and North American population (P=0.054).

Association between HLA-B27 and age at onset

In the total included axSpA population, the median age at onset of axial symptoms of HLA-B27-positive patients was significantly lower than of HLA-B27-negative patients [25 years (IQR 19–32) vs 31 (22–39); P<0.001]. This difference was found in each of the geographical regions: Asia 23 years (IQR 19–30) vs 28 (20–36), P=0.009; Europe and North America 25 (19–32) vs 33 (22–40), P<0.001; Latin America 26 (19–36) vs 40 (26– 44), P<0.001; Middle East and North Africa 25 (19–32) vs 29 (22–39), P=0.008 (Fig. 1).

Linear regression models showed a significant effect of HLA-B27 status on the age at onset of axial symptoms in the total study population (P<0.001) and all geographical regions (Asia, P=0.006; Europe and North America, P<0.001; Latin America, P<0.001; Middle East and North Africa, P=0.005).

Multivariable model

First, we tested whether there was collinearity between gender and HLA-B27 status, which was not the case, meaning gender and HLA-B27 did not have a linear relationship and could both be included in the linear regression model. In the multivariable model in the total included axSpA population, both HLA-B27 and male gender were associated with earlier disease onset. However, when stratified by region, an additional statistically significant effect of male gender independent of HLA-B27 was only found in Asia (Table 3), but a similar trend could be observed in all regions.

Table 2 Characteristics of the axial spondyloarthritis patients from the ASAS-PerSpA study analysed in this study, stratified by age at onset.

	Total *N=2,579*	**Age at onset <45** *N=2,368*	**Age at onset ≥45** *N=211*
Gender, male	69%	70%	51%
Age, median (IQR)	40 (31-51)	39 (31-48)	58 (53-64)
Symptom duration (yrs), median (IQR)	11 (5-19)	11 (5-20)	6 (3-11)
HLA-B27 positive	79%**	80%**	60%***
IBP ASAS definition[†]	94%	95%	87%
Positive family history	34%	35%	25%
Peripheral arthritis	44%	43%	50%
Enthesitis	45%	45%	49%
Dactylitis	6%	6%	7%
Psoriasis	8%	8%	10%
IBD	5%	5%	7%
Acute anterior uveitis	22%	23%	17%
Elevated CRP	70%	71%	61%
Sacroiliitis on pelvic radiographs[‡]	78%	79%	68%
Sacroiliitis on pelvic MRI[‡]	82%***	83%***	76%***
Number of SpA features[§], mean (SD)	4 (2)	4 (2)	4 (2)
Use of bDMARD	33%*	33%*	30%*
Use of NSAID	99%*	99%*	97%*
Radiographic axSpA	79%	80%	73%
LoC regarding axSpA diagnosis, mean (SD)	8 (3)	8 (3)	7 (3)

* 5-10% missing values, ** 10-20% missing values, ***20-40% missing values

[†] 4 out of 5 of the following features: onset before the age of 40, insidious onset, improvement with exercise, no improvement with rest, pain at night[21]

[‡] Based on reading of local radiologists

[§] Excluding HLA-B27 status and sacroiliitis on imaging

ASAS, Assessment of SpondyloArthritis international Society; **axSpA**, axial spondyloarthritis; **bDMARD**, biological Disease Modifying Anti-Rheumatic Drug; **CRP**, C-reactive protein; **HLA-B27**, Human Leucocyte Antigen B27; **IBD**, Inflammatory Bowel Disease; **IBP**, Inflammatory Back Pain; **IQR**: Inter-Quartile Range; **LoC**, Level of Confidence regarding the diagnosis; **MRI**, Magnetic Resonance Imaging; **NSAIDs**, Non-Steroidal Anti Inflammatory Drugs; **SpA**, Spondyloarthritis.

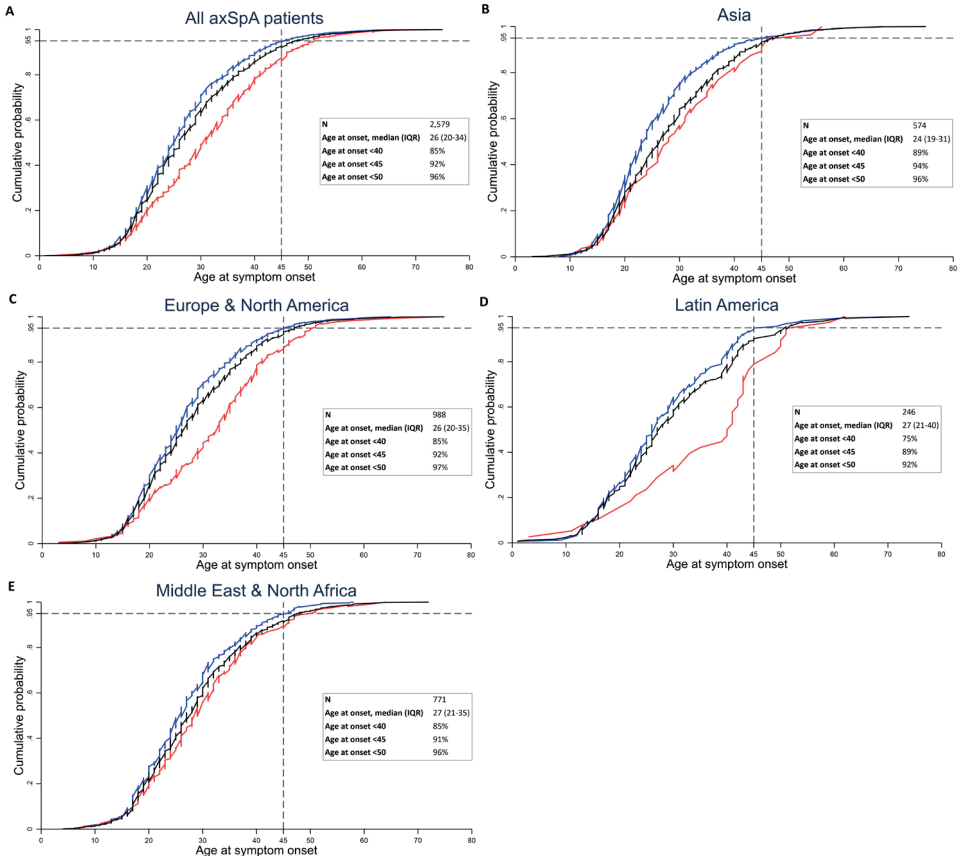

Figure 1 Cumulative distribution of the age at onset of axial symptoms, stratified by HLA-B27 status. **A** all included axial spondyloarthritis patients; **B** Asia; **C** Europe & North America; **D** Latin America; and **E** Middle East & North Africa. The black lines represent all patients in each region, the blue lines represent HLA-B27 positive patients, and the red lines represent the HLA-B27 negative patients. The horizontal dashed line represents the 95% point, and the vertical dashed line represents an age at onset of 45 years. IQR: Inter-Quartile Range

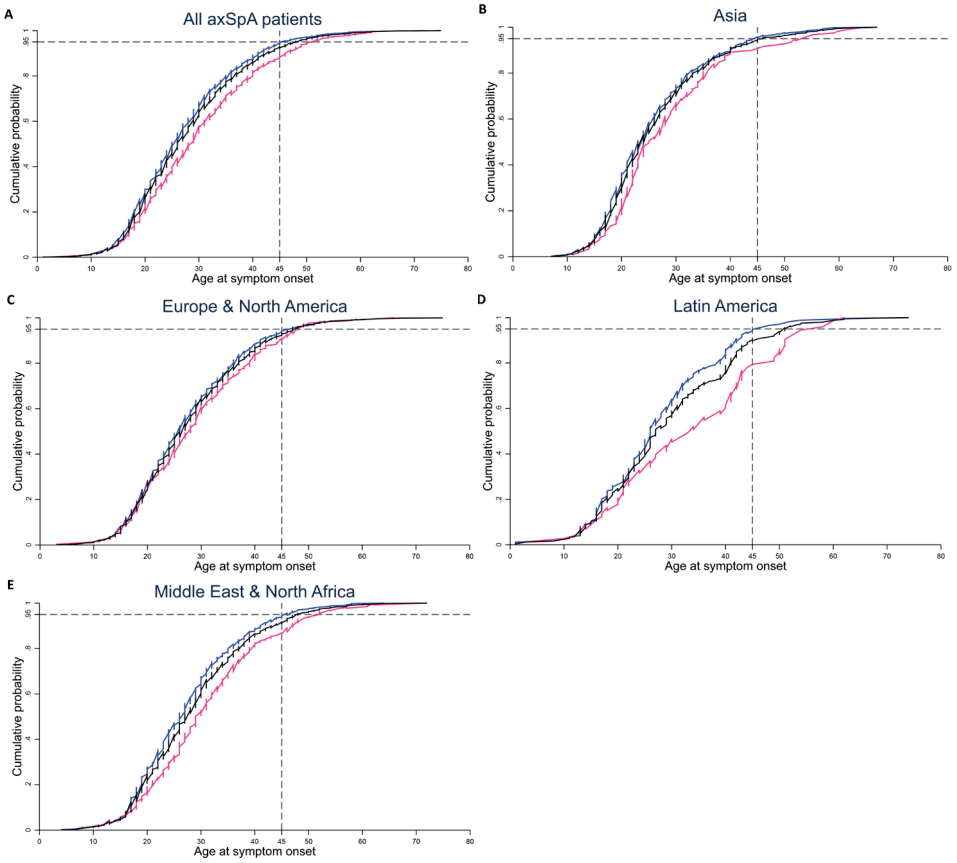

Figure 2 Cumulative distribution of the age at onset of axial symptoms, stratified by gender **A** all included axial spondyloarthritis patients; **B** Asia; **C** Europe & North America; **D** Latin America; and **E** Middle East & North Africa. The black lines represent all patients in each region, the blue lines represent male patients, and the pink lines represent the female patients. The horizontal dashed line represents the 95% point, and the vertical dashed line represents an age at onset of 45 years.

Table 3 Multivariable models assessing the effect of HLA-B27 & gender on age at onset of axial symptoms

	Multivariable linear regression	
	β (95% CI)	**p-value**
Total study population (n=2,063)		
HLA-B27		
Negative	*Ref.*	
Positive	**-4.35 (-5.45 ; -3.25)**	**<0.001**
Gender		
Female	*Ref.*	
Male	**-1.71 (-2.69 ; -0.74)**	**0.001**
Asia (n=525)		
HLA-B27		
Negative	*Ref.*	
Positive	**-3.68 (-6.44 ; -0.92)**	**0.009**
Gender		
Female	*Ref.*	
Male	**-2.23 (-4.34 ; -0.11)**	**0.039**
Europe & North America (n=862)		
HLA-B27		
Negative	*Ref.*	
Positive	**-5.18 (-6.88 ; -3.48)**	**<0.001**
Gender		
Female	*Ref.*	
Male	-0.92 (-2.38 ; 0.53)	0.215
Latin America (n=195)		
HLA-B27		
Negative	*Ref.*	
Positive	**-7.30 (-11.59 ; -3.00)**	**0.001**
Gender		
Female	*Ref.*	
Male	-3.44 (-7.11 ; 0.23)	0.066
Middle East & North Africa (n=481)		
HLA-B27		
Negative	*Ref.*	
Positive	**-2.44 (-4.36 ; -0.53)**	**0.013**
Gender		
Female	*Ref.*	
Male	-1.58 (-3.50 ; 0.34)	0.106

CI: confidence interval; Statistically significant associations are printed in **bold**

DISCUSSION

This study provides the first cumulative distribution of age at onset of axial symptoms in axSpA patients across the globe, showing that the vast majority of patients with axSpA have an age at onset before the age of 45 years in all parts of the world, which is consistent with the ASAS classification criteria for axSpA.

This study adds an important global perspective to what has been previously reported[1, 2, 4, 5]. Akin to what has been shown in previous studies[1, 2, 4], we found that patients with HLA-B27-negative disease had a significantly higher age at symptom onset than those with HLA-B27-positive disease and this held true in all geographical regions.

Contrary to Feldtkeller et al.[1], we showed a higher age at onset of axial symptoms in female patients compared to their male counterparts, which is in line with findings from other studies[2, 4, 5, 22, 23]. This difference may be partly explained by the fact that female patients were underrepresented in the study conducted by Feldtkeller et al.[1], possibly as a result of underdiagnosis of r-axSpA in women in the past[24]. Similar to Chung et al.[2], we found an additional effect of male gender and HLA-B27 on age at onset in multivariable analysis in the total included axSpA population, indicating a different association between HLA-B27 and age at onset for male and female patients. However, in multivariable analysis stratified by geographical region, an additional effect of male gender and HLA-B27 was only found in Asia. The current study adds important information to the work previously published, as the data presented in this study include patients with axSpA from across the globe. Also, patients had a rheumatologist-confirmed diagnosis rather than a self-reported diagnosis.
The precise pathophysiological mechanisms underlying axSpA remain unclear, but as different types of HLA-B27 are found in different parts of the world (e.g. HLAB*27:05 in Europe and HLA-B*27:04 in Asia) and the association between HLA-B27 and axSpA varies between races[19], one might have expected to find more variation in age at onset and its association with HLA-B27 across geographical regions. Race was unavailable in the ASAS-PerSpA dataset, yet we expect the majority of the patients included in each geographical region to identify with its most prominent race, hence a clear effect of race would have been seen in the data. Additionally, many other factors are thought to have an influence on the occurrence of axSpA, such as other genetic factors and differences in the human microbiome and environmental factors, such as smoking[5, 25], which makes the relative consistency in age at onset all the more intriguing.

A potential limitation of this study is the fact that data were collected cross-sectionally based on patient records and patient-reported information, which has resulted in some missing data, especially regarding HLA-B27 status, as this was not specifically analysed for this study. Nonetheless, all geographical regions contained both patients with HLA-B27-positive and-negative disease and patients whose HLA-B27 status was unknown were not different than those with non-missing data (data not shown).

CONCLUSION

Irrespective of geographical region, the majority of axSpA patients had an age at onset of axial disease before the age of 45 years and being an HLA-B27 carrier and male gender were associated with earlier disease onset around the globe, yet an independent effect of male gender on top of HLA-B27 was only found in Asian patients. These results provide crucial data for diagnosis, classification and policies aimed at improving recognition of axSpA.

SUPPLEMENTARY DATA

Supplementary data are published online on the website of Rheumatology (Oxford)

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