Classification Criteria for Spondyloarthritis/HLA-B27-Associated Anterior Uveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,4,*]

• PURPOSE: The purpose of this study was to determine classification criteria for spondyloarthritis/HLA-B27-associated anterior uveitis

• DESIGN: Machine learning of cases with spondyloarthritis/HLA-B27-associated anterior uveitis and 8 other anterior uveitides.

• METHODS: Cases of anterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set. Machine learning using multinomial logistic regression was used in the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the anterior uveitides. The resulting criteria were evaluated in the validation set.

• RESULTS: A total of 1,083 cases of anterior uveitides, including 184 cases of spondyloarthritis/HLA-B27-associated anterior uveitis, were evaluated by machine learning. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% CI: 92.4-98.6). Key criteria for spondyloarthritis/HLA-B27-associated anterior uveitis included 1) acute or recurrent acute unilateral or unilateral alternating anterior uveitis with either spondyloarthritis or a positive test result for HLA-B27; or 2) chronic anterior uveitis with a history of the classic course and either spondyloarthritis or HLA-B27; or 3) anterior uveitis with both spondyloarthritis and HLA-B27. The misclassification rates for spondyloarthritis/HLA-B27-associated anterior uveitis were 0% in the training set and 3.6% in the validation set.

• CONCLUSIONS: The criteria for spondyloarthritis/HLA-B27-associated anterior uveitis had a low misclassification rate and appeared to perform well enough for use in clinical and translational research. (Am J Ophthalmol 2021;228: 117–125. © 2021 Elsevier Inc. All rights reserved.)

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Spondyloarthritis (SpA) refers to a spectrum of inflammatory arthritides with overlapping features that include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and arthritis related to inflammatory bowel disease.[1,2] The prevalence of SpA is estimated at ~1.5%-2.0%, and that of ankylosing spondylitis at ~0.5%-1.0%.[2] The diseases are linked to the HLA allele HLA-B27 with population disease frequency variation due, at least in part, to the population gene frequency variation of HLA-B27. A total of 90%-95% of white patients with ankylosing spondylitis will possess HLA-B27 and 70%-80% of patients with reactive arthritis, compared to a general white population gene frequency for HLA-B27 of ~8%. The frequency of HLA-B27 among patients with psoriatic arthritis and inflammatory bowel disease-associated arthritis (enteropathic arthritis) is lower, ~24% and 7%, respectively, but substantially higher among patients with psoriatic spondyli-

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TABLE 1. ASAS Classification Criteria for Axial SpA In Patients With Back Pain ≥3 Months and Age of Onset <45 Years

Sacroiliitis on Imaging Plus ≥1 SpA Feature	OR	HLA-B27 Plus ≥2 SpA Features
SpA features: • Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn disease/ulcerative colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP		Sacroiliitis on imaging: • Active inflammation on MRI highly suggestive of sacroiliitis with SpA or • Definite radiographic sacroiliitis according to the modified New York criteria

ASAS = Assessment of SpondyloArthritis international Society; MRI = magnetic resonance imaging; CRP = C-reactive protein; NSAIDs = non-steroidal anti-inflammatory drugs; SpA = spondyloarthritis.
Table 1 was adapted from Rudwaleit and associates.[7]

tis and spondylitis/sacroiliitis with inflammatory bowel disease, ~60%-70%.[1]

Predominant axial involvement (axial SpA) is the hallmark of ankylosing spondylitis and is characterized by inflammatory back pain with marked morning stiffness and worsening of symptoms with inactivity. Sacroiliac joint involvement is classic, and there may be variable peripheral joint involvement as well. Peripheral SpA typically involves non-axial joints with limited axial involvement and includes reactive arthritis, psoriatic arthritis, and inflammatory bowel disease-related arthritis.[1,2]

Classification criteria were first developed for ankylosing spondylitis in 1961 with the Rome criteria, with subsequent development of the New York criteria and the modified New York criteria in 1984. The New York and modified New York criteria require radiographic demonstration of sacroiliitis. Early radiographic changes are difficult to detect and may take up to 10 years after disease onset to become evident. Computed tomographic (CT) imaging and magnetic resonance imaging (MRI) are more sensitive than conventional radiography. CT is superior for detecting bony involvement, and MRI is preferred for soft tissue inflammation.[2-4] Classification criteria for psoriatic arthritis were first proposed by Moll and Wright in 1973 and evolved over time into the CASPAR criteria, published in 2006.[2,5]

More recently, SpA has been divided into axial SpA and peripheral SpA, based on the presence or absence of axial (spinal and sacroiliac) arthritis. The Assessment of SpondyloArthritis International Society (ASAS) published criteria for axial SpA in 2009, which divided axial SpA into radiographic and non-radiographic axial SpA, and for peripheral SpA in 2011.[2,6-8] The ASAS criteria for axial SpA are outlined in Table 1 and for peripheral SpA in Table 2. The ASAS criteria are more inclusive than previous sets as radiologic changes are not required.

TABLE 2. ASAS Classification Criteria for Peripheral SpA

Arthritis (peripheral) or enthesitis or dactylitis
PLUS ≥1 Spondyloarthritis feature • Uveitis • Psoriasis • Crohn disease/ulcerative colitis • Preceding infection • HLA-B27 • Sacroiliitis on imaging OR ≥2 other spondyloarthritis features • Arthritis • Enthesitis • Dactylitis • Inflammatory back pain • Family history for SpA

ASAS = Assessment of SpondyloArthritis international Society.
Table 2 was adapted from Rudwaleit and associates.[8]

TABLE 3. Characteristics of Cases with Spondyloarthritis/HLA-B27-associated Anterior Uveitis

Characteristic	Result
Number cases	184
Demographics	
Median IQR (25th 75th) age, y	37 (30, 46)
Age category, y %	
≤16	4
17–50	76
51–59	11
≥60	10
Men, %	54
Women, %	46
Race/ethnicity, %	
White, non-Hispanic	73
Black, non-Hispanic	4
Hispanic	2
Asian, Pacific Islander	13
Other	3
Missing/unknown	5
Uveitis history	
Uveitis course, %	
Acute, monophasic	15
Acute, recurrent	61
Chronic	17
Indeterminate	8
Laterality, %	
Unilateral	60
Unilateral, alternating	36
Bilateral	4
Ophthalmic examination	
Cornea	
No keratitis	100
Keratitis	0
Keratic precipitates, %	
None	0
Fine	41
Round	54
Stellate	5
Mutton-fat	0
Other	0
Anterior chamber cells, %	
Grade ½+	8
1+	23
2+	35
3+	24
4+	10
Hypopyon, %	10
Anterior chamber flare, %	
Grade 0	28
1+	36
2+	18
3+	7
4+	11

(*continued on next page*)

TABLE 3. (*continued*)

Characteristic	Result
Iris, %	
Normal	61
Posterior synechiae	38
Sectoral iris atrophy	1
Patchy iris atrophy	1
Diffuse iris atrophy	0
Heterochromia	0
IOP-involved eyes	
Median IQR (25th, 75th) mm Hg	13 (12, 16)
Proportion patients with IOP >24 mm Hg in either eye, %	2
Vitreous cells, %	
Grade 0	68
½+	17
1+	12
2+	2
3+	1
4+	0
Systemic disease, %	
Spondyloarthritis	53
Psoriasis	6
Inflammatory bowel disease	2
Laboratory	
Positive HLA-B27, % [a]	97

IOP = intraocular pressure; IQR = interquartile range.
[a] 179 of 184 patients tested positive.

Among the most common extra-articular features of SpA is uveitis.[1,2] Estimates of the cumulative risk of uveitis among patients with ankylosing spondylitis run as high as 55% but typically are reported as ~25%. The risk appears similar among patients with reactive arthritis but lower in the range of 10%-20% for enteropathic arthritis and psoriatic arthritis.[1] The typical pattern for SpA-associated uveitis is a recurrent acute, unilateral, or unilateral alternating anterior uveitis.[1,9] This type of uveitis is shared with SpA HLA-B27 as a risk factor. Approximately 60% of patients with recurrent acute unilateral anterior uveitis will be HLA-B27-positive, and 80% of those with recurrent acute unilateral alternating anterior uveitis will be HLA-B27-positive.[9] Among patients with uveitis and HLA-B27, the prevalence of SpA is estimated at 58%-78%.[10-12] In one 11-year nationwide study of incidence, the incidence of ankylosing spondylitis among patients with acute anterior uveitis was 121.5/100,000 person years, which was ~17-fold greater than among patients without acute anterior uveitis.[13]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developed classification criteria for 25 of the most common uveitides using a formal approach to development of classification criteria.[14-20] Among the uveitides studied was SpA/HLA-B27-associated anterior uveitis.[15,17,20]

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in 4 phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[16-18,20]

• **INFORMATICS:** As previously described, the consensus-based informatics phase permitted development of a standardized vocabulary and a standardized, menu-driven hierarchical case collection instrument.[16]

• **CASE COLLECTION AND CASE SELECTION:** Information was entered into the SUN preliminary database by the 76 contributing investigators for each disease as previously described.[18,20] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying articles.[18,20] Because the goal was to develop classification criteria, only cases with a supermajority agreement (>75%) that the case was the disease were retained in the final database (ie, were "selected").

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of cases) and

TABLE 4. Comparison of Characteristics of Cases with Spondyloarthritis/HLA-B27-associated Acute Versus Chronic Anterior Uveitis

Characteristic	Acute Anterior Uveitis[a]	Chronic Anterior Uveitis[b]	*P* Value
Number of cases	155	29	
Demographics			
Median IQR (25th 75th) age, y	37 (29, 46)	37 (35, 40)	.78
Men, %	52	65	.17
Women, %	48	35	.17
Race/ethnicity, %			.09
White, non-Hispanic	73	86	
Black, non-Hispanic	4	4	
Hispanic	0	0	
Asian, Pacific Islander	16	0	
Other	3	4	
Missing/unknown	4	6	
Uveitis history			
Laterality, %			<.001
Unilateral	56	79	
Unilateral, alternating	43	0	
Bilateral	1	21	
Ophthalmic examination			
Keratic precipitates, %			.79
None	40	45	
Fine	55	48	
Other	5	7	
Anterior chamber cells, %			.52
≤2+	64	79	
>2+	36	21	
Hypopyon, %	10	14	.51
Iris, %			.19
Normal	65	52	
Posterior synechiae	35	48	
IOP-involved eyes	14 (13, 17)	15 (13, 18)	.31
Median IQR (25th, 75th) mm Hg			
Vitreous cells, %			.52
Grade 0	68	66	
≥½+	32	34	
Systemic disease, %			
Spondyloarthritis (axial or peripheral)	48	72	.03
Inflammatory bowel disease	3	7	
Laboratory			
Positive HLA-B27, %	98	97	.61

IOP = intraocular pressure; IQR = interquartile range.

[a]Includes 113 cases with recurrent acute anterior uveitis and 42 cases with a single episode of acute anterior uveitis.

[b]Includes 8 cases with a history of acute anterior uveitis and a crescendo pattern into chronic anterior uveitis

a validation set (~15% of cases) for each disease, as described in the accompanying article.[20] Machine learning was used in the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set. For both the training set and the validation set, the misclassification rates were calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm compared to the consensus diagnosis. For SpA/HLA-B27-associated anterior uveitis, the diseases against which it was evaluated were cytomegalovirus (CMV) anterior uveitis; herpes simplex virus (HSV) anterior uveitis; vari-

TABLE 5. Classification Criteria for Spondyloarthritis/HLA-B27-associated Anterior Uveitis

Criteria
1. Evidence of anterior uveitis
a. Anterior chamber cells
b. If anterior vitreous cells are present, severity is less than anterior chamber inflammation
AND either (both #2 and #3) OR #4
2. Characteristic uveitis course
a. Acute or recurrent acute, unilateral or unilateral alternating course OR
b. Chronic course with a history of a recurrent acute, unilateral or unilateral alternating course evolving into chronic course
AND
3. ASAS-defined spondyloarthritis (axial or peripheral) and/or HLA-B27-positive
OR
4. Chronic uveitis with both ASAS-defined spondyloarthritis (axial or peripheral) AND HLA-B27-positive
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)
3. Aqueous specimen PCR positive for cytomegalovirus, herpes simplex virus or varicella zoster virus

ASAS = Assessment of SpondyloArthritis international Society; PCR = polymerase chain reaction.
[a]ASAS criteria for axial spondyloarthritis or peripheral spondyloarthritis.[7,8] See Tables 1 and 2.

cella zoster virus (VZV) anterior uveitis; juvenile idiopathic arthritis (JIA)-associated anterior uveitis; tubulointerstitial nephritis with uveitis (TINU); Fuchs uveitis syndrome; sarcoidosis-associated anterior uveitis; and syphilitic anterior uveitis.

• **COMPARISON BETWEEN CASES WITH ACUTE ANTERIOR UVEITIS AND CHRONIC ANTERIOR UVEITIS:** A comparison between cases with acute anterior uveitis and those with chronic anterior uveitis for categorical variables was performed using the χ^2 test or the Fisher exact test if a cell was less than 5. For categorical variables with multiple grades, grades above and below the median were compared. For continuous variables, the Wilcoxon rank sum test was used. *P* values are nominal and 2-sided.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

RESULTS

A total of 251 cases of SpA/HLA-B27-associated anterior uveitis were collected, and 184 (74%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of SpA/HLA-B27-associated anterior uveitis were compared to cases of other anterior uveitides, including 89 cases of CMV anterior uveitis, 123 cases of VZV anterior uveitis, 146 cases of Fuchs uveitis syndrome, 202 cases of JIA-associated anterior uveitis, 101 cases of HSV anterior uveitis, 94 cases of TINU, 112 cases of sarcoidosis-associated anterior uveitis, and 32 cases of syphilitic anterior uveitis. The characteristics at presentation to a SUN Working Group Investigator of cases with SpA/HLA-B27 anterior uveitis are listed in Table 3. A comparison between cases with acute or recurrent acute anterior uveitis and those with chronic anterior uveitis is listed in Table 4. The criteria developed after machine learning are listed in Table 5. Key features of the criteria include anterior uveitis with either an acute or recurrent acute course or, if a chronic course, a history of a recurrent acute course evolving into a chronic course, and the presence of either HLA-B27 or a SpA or anterior uveitis in the presence of both HLA-B27 and SpA. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% CI: 92.4-98.6).[20] The misclassification rate for SpA/HLA-B27-associated anterior uveitis in the training set was 0% and 3.6% in the validation set.

DISCUSSION

Numerous case series have documented the overlapping relationships among SpA, HLA-B27, and acute anterior uveitis.[1,9-13] Nevertheless, HLA-B27 is a risk factor, and these diseases are not simple Mendelian genetic disorders.

Even among whites with ankylosing spondylitis, the most closely linked SpA to HLA-B27, 5%-10% will be HLA-B27-negative.[1] With a population frequency for HLA-B27 of ~8% and an ankylosing spondylitis prevalence of ~1%, it is the minority of patients with HLA-B27 who will develop SpA. Furthermore, among patients with other defined uveitides, 8% would be expected to be HLA-B27-positive by chance alone. Hence, the presence of HLA-B27 alone is not diagnostic of an SpA/HLA-B27-associated anterior uveitis, and the criteria can be distilled as requiring anterior uveitis and 2 of the 3 features: classic presentation, HLA-B27, or SpA.

Although most cases had the classic course, namely acute or recurrent acute, unilateral or unilateral alternating, anterior uveitis, ~15% of patients in the SUN data base had a chronic uveitis upon presentation to a SUN investigator, a result seen in other large cohorts of patients with SpA.[21] Several of the cases in the SUN database had a history of a classic pattern that evolved over time into a chronic uveitis, a phenomenon which has been described previously.[11] The comparison between acute and chronic uveitis suggested that chronic uveitis cases were more likely to have a diagnosis of SpA. The greater frequency of SpA among patients with chronic uveitis and SpA/HLA-B27-associated anterior uveitis may reflect the uncertainty of the relationship between HLA-B27 alone and chronic anterior uveitis (associated disease vs. chance) in the absence of SpA. There was a sentiment among the case selection committee that patients with psoriatic arthritis were more likely to have atypical SpA/HLA-B27-associated uveitis, namely chronic or bilateral disease, which appeared to be correct when the data were reviewed, but the data set lacked sufficient power for formal analysis of that impression.

The case collection phase used retrospective data, the diagnosis of SpA was a clinical one, and likely did not necessarily use the ASAS criteria. The ASAS criteria were developed to enable earlier diagnosis of SpA, as they do not require radiographic confirmation of sacroiliitis for axial SpA, which can take years to develop. Although it could not verified that all cases included in the SpA/HLA-B27 anterior uveitis database and identified as having SpA would have fulfilled the ASAS criteria, criteria for its diagnosis are needed going forward, and the ASAS criteria[6-8] were chosen by the SUN Working Group.

Although classically associated with endophthalmitis and Behçet disease, hypopyon can be seen with severe attacks of SpA/ HLA-B27-associated anterior uveitis. [22,23] One study estimated the 10-year incidence of hypopyon uveitis among patients with HLA-B27-associated uveitis to be 17%.[23] Risk factors for hypopyon uveitis included Behçet disease (adjusted relative risk [RR]: 5.30), SpA (RR: 2.86), and HLA-B27 (RR: 2.04).[23] In the United States, hypopyon uveitis is seen most often among patients with SpA/HLA-B27 anterior uveitis, whereas in regions where Behçet disease is more prevalent than in the United States, it will be seen more often with Behçet disease.[22,23] Nevertheless, because of its presence in several uveitides, hypopyon does not appear to be a discriminatory factor in classifying the uveitides.

The presence of any of the exclusions in Table 5 suggests an alternate diagnosis, and SpA/HLA-B27-associated anterior uveitis should not be diagnosed in their presence. In prospective studies, many of those tests will be performed routinely and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of those tests may have been performed. Hence, the presence of an exclusionary criterion excludes SpA/HLA-B27-associated anterior uveitis, but the absence of such testing does not exclude the diagnosis of SpA/HLA-B27-associated anterior uveitis if the criteria for the diagnosis are met.

Classification criteria are used to diagnose individual diseases for research purposes.[19] Classification criteria differ from clinical diagnostic criteria in that, although both seek to minimize misclassification, when a tradeoff is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[19] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process that was used did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because this study was focused on developing classification criteria and because the typical agreement between 2 uveitis experts on diagnosis was moderate at best,[18] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases that clinicians would diagnose with SpA/HLA-B27-associated uveitis may not be so classified by classification criteria. The selection of cases during the case selection phase of cases that achieved supermajority agreement on the diagnosis for inclusion in the final database was used in part because the study was developing classification criteria.

In conclusion, the criteria for SpA/HLA-B27-associated anterior uveitis outlined in Table 5 appear to perform sufficiently well for use as classification criteria in clinical research.

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