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Ocular Signs and Testing Most Compatible with Sarcoidosis-Associated Uveitis: A Latent Class Analysis

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Purpose: This study aims to explore the potential subgroups of sarcoidosis-associated uveitis (SAU) within a multicenter cohort of uveitis participants.

Design: Cross-sectional study.

Participants: A cohort of 826 uveitis patients from a uveitis registry from 19 clinical centers in 12 countries between January 2011 and April 2015.

Methods: We employed a latent class analysis (LCA) incorporating recommended tests and clinical signs from the revised International Workshop on Ocular Sarcoidosis (IWOS) to identify potential SAU subgroups within the multicenter uveitis cohort. Additionally, we assessed the performance of the individual tests and clinical signs in classifying the potential subclasses.

Main Outcome Measures: Latent subtypes of SAU.

Results: Among 826 participants included in this analysis, the 2-class LCA model provided a best fit, with the lowest Bayesian information criteria of 7218.7 and an entropy of 0.715. One class, consisting of 548 participants, represented the non-SAU, whereas the second class, comprised of 278 participants, was most representative of SAU. Snowballs/string of pearls vitreous opacities had the best test performance for classification, followed by bilaterality and bilateral hilar lymphadenopathy (BHL). The combination of 4 tests with the highest classification importance, including snowballs/string of pearls vitreous opacities, periphlebitis and/or macroaneurysm, bilaterality, and BHL, demonstrated a sensitivity of 84.8% and a specificity of 95.4% in classifying the SAU subtypes. In the exploratory analysis of the 3-class LCA model, which had comparable fit indices as the 2-class model, we identified a candidate non-SAU subtype, candidate SAU subtype with pulmonary involvement, and a candidate SAU with less pulmonary involvement.

Conclusions: Latent class modeling, incorporating tests and clinical signs from the revised IWOS criteria, effectively identified a subset of participants with clinical features indicative of SAU. Though the sensitivity of individual ocular signs or tests was not perfect, using a combination of tests provided a satisfactory performance in classifying the SAU subclasses identified by the 2-class LCA model. Notably, the classes identified by the 3-class LCA model, including a non-SAU subtype, an SAU subtype with pulmonary involvement, and an SAU subtype with less pulmonary involvement, may have potential implication for clinical practice, and hence should be validated in further research.

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Sarcoidosis, a significant cause of noninfectious uveitis, can be challenging to diagnose. The heterogeneous manifestations of sarcoidosis-associated uveitis (SAU) may be related, in part, to age and geographic region and may overlap with other conditions, such as tuberculosis.[1] While the use of biopsy of affected tissue to identify the classic granuloma has been considered the diagnostic gold standard for sarcoidosis, there are situations where obtaining tissue for biopsy may not be feasible or appropriate, even though a high suspicion for sarcoidosis may exist based on clinically compatible features. Indeed, the most important clinical signs and diagnostic tests for SAU were codified by the International Workshop on Ocular Sarcoidosis (IWOS) in 2009 and were subsequently revised in 2019.[2,3] The consensus group for IWOS consisted of a panel of uveitis experts from around the globe who convened to define the criteria. The collaborative nature of this approach offered advantages;

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experts gathered together with a dedicated focus on defining the criteria and collectively assessing the value of each criterion in relation to SAU.[2] However, in consensus meetings, there may be bias in questionnaire design, vulnerability in determining who qualifies as an expert, potential bias in selecting participants, and panel judgments that may be influenced by certain panel members. Specific decision-makers, particularly those who are prominent, vocal, or dominant, can introduce biases, and group decision-making can be prone to failures such as "group thinking."[4] This collective mentality may overlook independent ideas or suggestions from individual participants, leading to a preference for ideas that are most agreeable to the majority. In light of these challenges, diseases that do not have a diagnostic gold standard test, like SAU, have undergone significant classification revisions relying initially on probabilistic modeling or clustering algorithms.[5–10]

There is a growing need for data-driven classification criteria for diseases. Ideally, there would be a single diagnostic test or sign that would accurately differentiate between individuals with a particular disease state and those without it or differentiate between different disease subtypes (such as mild, moderate, and severe). However, the utilization of different clinical signs or tests in combination, as well as variations in reference standards among individual clinicians, societies, or regions, may introduce bias in the quantitative assessment of test performance and disease prevalence estimates in different populations. Unsupervised probabilistic modeling algorithms, such as latent class analysis (LCA), offer a possible solution by agnostically identifying latent or hidden disease classes in a population.[11] The approach has proven beneficial in identifying subtypes of diverse and complex diseases, including trachoma and dry eye disease.[12–14] In this study, therefore, we applied LCA, incorporating the recommended tests and clinical signs from the revised IWOS, to explore the potential SAU subclasses within a cohort of uveitis participants. Subsequently, we evaluated the test performance of the included tests and clinical signs in identifying potential SAU classes by utilizing the class membership assigned by the LCA.

Methods

We used data from a cohort of uveitis patients included in a retrospective uveitis registry from 19 tertiary clinical centers in 12 countries between January 2011 and April 2015. The study procedures were approved by institutional review board at the University of California, San Francisco, and local research sites. The research adhered to the tenets of the Declaration of Helsinki. Written informed consent was not required because of the retrospective nature of the study. Details of the study protocol have been previously published.[15] Briefly, 1065 participants aged between 4 and 93 years who were referred for uveitis evaluation at each clinical center and were followed up at 6 months and 1 year were included. Specifically, clinics were asked to submit up to 100 consecutive uveitis cases identified through recent retrospective chart review. Information on participants' demographics and systemic health conditions was collected from the time of their initial presentation. Participants had a full eye exam (slit lamp, gonioscopy, and dilated funduscopy) and underwent laboratory testing and chest radiographic imaging at baseline. Laboratory and radiographic imaging results were only available upon return for the 6-month follow-up. Therefore, we restricted our analysis to only those participants who attended the 6-month follow-up in order to have a relatively complete dataset.

LCA

We identified potential SAU subgroups within our uveitis cohort using LCA, which is a probabilistic modeling designed to uncover qualitatively different subgroups, or latent groups or classes, within populations that share similar outward features. One of the advantages of LCA over other clustering modeling techniques is its ability to generate fit statistics, which helps determine the optimal number of clusters for a study population.[16] For our study, the binary indicator variables for the LCA models were selected a priori based on the revised IWOS criteria, which is comprised of ocular signs (including mutton-fat keratic precipitates, iris nodules, trabecular meshwork nodules, tent-shaped peripheral anterior synechia, snowballs/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions, nodular and/or segmental periphlebitis and/or macroaneurysm, optic disc nodules, solitary choroidal nodule, and bilaterality) and systemic investigation results (including bilateral hilar lymphadenopathy [BHL] by chest x-ray and/or chest computed tomography scan, negative tuberculin test, elevated serum angiotensin-converting enzyme, and elevated serum lysozyme). Tests such as abnormal CD4/CD8 ratio in bronchoalveolar lavage (BAL) fluid and gallium scintigraphy were not included in the models due to approximately 90% missing values, as these tests were infrequently ordered at all sites. Furthermore, 2 other tests recommended by the revised IWOS, namely lymphopenia and parenchymal lung changes consistent with sarcoidosis, were not available in our dataset because our study period was before revised IWOS criteria were released.

Models with 1 to 6 classes were applied to the data, and the performance of each model was evaluated using several fit indices, including Bayesian information criteria (BIC), sample size–adjusted BIC, Akaike information criteria, and relative entropy. Bootstrapped likelihood ratio test was employed to compare the goodness of fit of the model with k classes versus that with k − 1 classes. The final model was selected based on model performance, class sizes, and most importantly, clinical interpretability.

The participants' demographic characteristics and test results were described by identified class, with the aim of identifying distinguishing features of each latent class. We considered the class with the lowest proportion of positive biopsy or BHL as the reference group, and the other classes therefore represented candidate subtypes of SAU. For each diagnostic test utilized in the LCA models, we calculated the test sensitivity for each subtype of SAU and specificity and computed 95% confidence intervals (CIs) using the Clopper–Pearson method. Additionally, we compared the diagnostic categories of SAU suggested by the revised IWOS criteria with the potential classes identified in our analysis. The revised IWOS criteria include a "definite" group, characterized by diagnosis supported by biopsy with compatible uveitis, a "presumed" group, defined as diagnosis not supported by biopsy, but BHL present with 2 intraocular signs, and a "probable" group, where the diagnosis is not supported by biopsy and BHL absent, but 3 intraocular signs and 2 SAU relevant systemic investigations are present.

Using each participant's class assignment as the indicator, we performed random forest analysis to select the most important classifiers for distinguishing latent classes. Our cohort was randomly split into a training set (70%) and a test set (30%). Missing values were imputed using the multiple imputation with chained equations. The 5 top classifiers with the highest variable

importance were entered in forward stepwise regression models. The performance of trained models was validated on the test dataset. The probability cutoff of class assignment was determined by the Youden index. Model quality was evaluated by generating receiver operating characteristic curves and calculating area under the curve, accuracy, sensitivity, specificity, and BIC. Calibration plot was applied to visualize the agreement between the predictions and observations.

Given that sarcoidosis disease characteristics in Japan differ remarkably from other regions, with a higher incidence of ocular and cardiac involvement, we performed a subgroup analysis by fitting the LCA models separately to Japanese participants and participants from other regions.[17] Further, we conducted an exploratory analysis to assess the prediction performance of regression models with only ocular signs or only laboratory investigations. In the event that the performance of alternative models was equally satisfactory as the selected model, we would conduct a sensitivity analysis to investigate those models.

All statistical analyses were performed using R (version 4.2.3). Latent class analysis models were conducted using the "poLCA" package.

Results

Our analysis included 826 participants with uveitis who presented at the 6-month follow-up and had accessible laboratory results. Using ocular signs and laboratory investigations, the LCA model with 2 classes demonstrated the best fit to the data, with the lowest BIC of 7218.7 (Table 1). Class 1 was comprised of 548 participants, while the remaining 278 participants were assigned to class 2. The average latent class posterior probability, which is the mean probability of the class model accurately predicting class membership for individuals, was 0.92 (standard deviation, 0.12) for class 1 and 0.91 (standard deviation, 0.13) for class 2.[18] However, the entropy of the 2-class model (0.715) did not reach 0.800, indicating that the classes were not clearly separated from each other. The *P* values of bootstrapped likelihood ratio test were all below the significance level, suggesting that the more complex models with additional latent classes were better fitting to the data than the simpler models with fewer latent classes, which is commonly seen in practical applications involving real-life data.[16]

Table 2 shows the demographic profiles of each class. Compared with class 1, class 2 had a higher proportion of participants who were of Asian descent, female, and had been diagnosed with sarcoidosis and/or the uveitis clinician suspected SAU. In class 1, only 3.6% of participants had positive BHL by chest x-ray and/or chest computed tomography scan, and 4.6% of participants had a positive biopsy from lung, lymph node, skin, or conjunctiva (Tables 2 and 3). In contrast, 47.8% and 30.2% of participants in class 2 had positive BHL and positive biopsy, respectively. Therefore, we proposed that class 1 represented the candidate non-SAU class, whereas class 2 represented the candidate SAU class. Indeed, participants in class 2 were more likely to exhibit clinical signs suggestive of SAU, including mutton-fat keratic precipitates, iris nodules, trabecular meshwork nodules, tent-shaped peripheral anterior synechia, snowballs/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions, nodular and/or segmental periphlebitis and/or macroaneurysm, and bilaterality. Optic disc nodules and/or solitary choroidal nodules were less frequently seen in our study population, and their frequencies did not differentiate between groups (Table 3). Concerning laboratory investigations, in addition to BHL and biopsy, abnormal accumulation of gallium-67 scintigraphy and abnormal findings of BAL fluid were more commonly observed in the candidate SAU class compared with the candidate non-SAU class; however, only a small proportion of participants had undergone these 2 examinations and therefore they were not included in the LCA models (Table S4, available at www.ophthalmologyscience.org). The candidate SAU class had a larger proportion of participants with negative tuberculin test results, elevated serum angiotensin-converting enzyme, and lysozyme (Table 2). Panuveitis was more commonly seen in the candidate SAU group (Table S4). The results of liver enzyme tests, including serum alkaline phosphatase, aspartate transaminase, alanine transaminase, γ-glutamyl transferase, and lactate dehydrogenase, were comparable between classes.

Using the 2 candidate class designations, we computed the sensitivity and specificity of each test included in the LCA models (Table 3). Our findings indicated that snowballs/string of pearls vitreous opacities had the best test performance with a sensitivity of 59.2% (95% CI, 53.0%−65.1%) and specificity of 95.3% (95% CI, 93.2%−97.0%). This was followed by bilaterality (sensitivity, 90.9% [95% CI, 86.8%−94%]; specificity, 58.7% [95% CI, 54.4%−62.9%]) and BHL (sensitivity, 53.8% [95% CI, 47.4%−60.2%]; specificity: 94.1%

Table 1. Fit Statistics for Latent Class Models with Different Prespecified Numbers of Classes

Model	BIC	aBIC	AIC	Entropy	Number of participants in each class					*P* Value*
1 class	7741.0	7699.7	7679.7	-	826					-
2 classes	7218.7	7133.0	7091.4	0.715	548	278				< 0.001
3 classes	7232.9	7102.7	7039.5	0.678	468	142	216			< 0.001
4 classes	7237.5	7062.8	6978.1	0.744	76	55	229	466		< 0.001
5 classes	7285.1	7065.9	6959.6	0.710	377	104	61	79	205	< 0.001
6 classes	7342.5	7078.9	6951.0	0.757	230	304	50	15	185	42	< 0.001

aBIC = sample size−adjusted Bayesian information criterion; AIC = Akaike information criterion; BIC = Bayesian information criterion.
**P* values are representative of bootstrapped likelihood ratio test.

[95% CI, 91.1%−96.4%]). In contrast, the Youden index of optic disc nodules and/or solitary choroidal nodule (2.8%) was just above 0. Almost all the tests had a specificity of approximately ≥ 90%, except for bilaterality and negative tuberculin test. However, only the sensitivity of bilaterality and negative tuberculin test exceeded 80%. When comparing the diagnostic categories of SAU suggested by IWOS to potential classes identified in our analysis, the definite group had a sensitivity of 83.2% (95% CI, 74.4%−89.9%) for identifying non-SAU (Table S5, available at www.ophthalmologyscience.org). However, the sensitivities of presumed and probable criteria were low.

To identify the most significant predictors of class assignment, we utilized random forest analysis to measure the importance of each diagnostic test included in the LCA model (Fig 1).The top 5 classifiers, namely snowballs/string of pearls vitreous opacities, periphlebitis and/or macroaneurysm, bilaterality, BHL, and chorioretinal peripheral lesions, were then entered in forward stepwise regression models. The combination of the first 4 tests yielded an area under the curve of 0.93 (95% CI, 0.92−0.95), and the combined test demonstrated a sensitivity of 84.8% and a specificity of 95.4% (Table S6, available at www.ophthalmologyscience.org). The calibration plot illustrated a high degree of agreement

Table 2. Demographic Profile of 826 Participants Included in the Latent Class Model and Stratified by 2 Candidate Classes of Sarcoidosis-Associated Uveitis

Characteristic	All Participants (%)	Non-SAU (%)	SAU (%)
Total	826 (100.0)	548 (66.3)	278 (33.7)
Sex			
Female	473 (57.3)	289 (52.7)	184 (66.2)
Male	350 (42.4)	256 (46.7)	94 (33.8)
Age (yrs)			
< 30	191 (23.1)	134 (24.5)	57 (20.5)
30−60	471 (57.0)	318 (58.0)	153 (55.0)
≥ 60	160 (19.4)	94 (17.2)	66 (23.7)
Region			
Belgium	34 (4.1)	9 (1.6)	25 (9.0)
China	52 (6.3)	50 (9.1)	2 (0.7)
Germany	9 (1.1)	6 (1.1)	3 (1.1)
India	153 (18.5)	111 (20.3)	42 (15.1)
Italy	96 (11.6)	65 (11.9)	31 (11.2)
Japan	174 (21.1)	79 (14.4)	95 (34.2)
Mexico	95 (11.5)	92 (16.8)	3 (1.1)
Spain	10 (1.2)	9 (1.6)	1 (0.4)
Taiwan	16 (1.9)	14 (2.6)	2 (0.7)
Tunisia	24 (2.9)	7 (1.3)	17 (6.1)
Turkey	32 (3.9)	4 (0.7)	28 (10.1)
United States	131 (15.9)	102 (18.6)	29 (10.4)
Race			
Asian	400 (48.4)	257 (46.9)	143 (51.4)
White	241 (29.2)	153 (27.9)	88 (31.7)
Others	140 (16.9)	116 (21.2)	24 (8.6)
Smoking status			
Unknown	173 (20.9)	101 (18.4)	72 (25.9)
Current	117 (14.2)	92 (16.8)	25 (9.0)
Past	77 (9.3)	44 (8.0)	33 (11.9)
Never	438 (53.0)	296 (54.0)	142 (51.1)
Duration of uveitis (yrs)			
< 0.5	214 (25.9)	134 (24.5)	80 (28.8)
0.5−1	64 (7.7)	37 (6.8)	27 (9.7)
1-5	128 (15.5)	74 (13.5)	54 (19.4)
> 5	61 (7.4)	34 (6.2)	27 (9.7)
Number of preexisting autoimmune diseases			
None	640 (77.5)	438 (79.9)	202 (72.7)
1	174 (21.1)	104 (19.0)	70 (25.2)
2	12 (1.5)	6 (1.1)	6 (2.2)
Any preexisting sarcoidosis	56 (6.8)	18 (3.3)	38 (13.7)
Any suspected SAU	311 (37.7)	103 (18.8)	208 (74.8)
Any respiratory symptoms	119 (14.4)	63 (11.5)	56 (20.1)
Positive biopsy	109 (13.2)	25 (4.6)	84 (30.2)

SAU = sarcoidosis-associated uveitis.

Table 3. Results and Test Performance of Clinical Signs and Laboratory Tests Included in the 2-Class Latent Class Model

Test	Overall (%)	Non-SAU (%)	SAU (%)	Specificity*	Sensitivity*	Youden Index
Clinical sign						
Mutton-fat KP	137 (16.6)	34 (6.2)	103 (37.1)	93.8% (91.4%–95.7%)	37.1% (31.4%–43.0%)	30.8%
Iris nodules	97 (11.7)	20 (3.6)	77 (27.7)	96.3% (94.4%–97.7%)	28.1% (22.9%–33.8%)	24.4%
Trabecular meshwork nodules	31 (3.8)	1 (0.2)	30 (10.8)	99.8% (98.7%–100.0%)	15.8% (10.9%–21.8%)	15.6%
Tent-shaped PAS	88 (10.7)	19 (3.5)	69 (24.8)	95.7% (93.4%–97.4%)	33.0% (26.7%–39.8%)	28.7%
Snowball/string of pearls vitreous opacities	183 (22.2)	25 (4.6)	158 (56.8)	95.3% (93.2%–97.0%)	59.2% (53.0%–65.1%)	54.5%
Multiple chorioretinal peripheral lesions	190 (23.0)	58 (10.6)	132 (47.5)	89.2% (86.3%–91.7%)	49.4% (43.3%–55.6%)	38.7%
Periphlebitis and/or macroaneurysm	140 (16.9)	16 (2.9)	124 (44.6)	97.0% (95.2%–98.3%)	46.1% (40.0%–52.3%)	43.1%
Optic disc nodule(s) and/or solitary choroidal nodule	30 (3.6)	15 (2.7)	15 (5.4)	97.2% (95.5%–98.4%)	5.5% (3.1%–9.0%)	2.8%
Bilaterality	471 (57.0)	222 (40.5)	249 (89.6)	58.7% (54.4%–62.9%)	90.9% (86.8%–94.0%)	49.6%
Laboratory test						
Abnormal BHL	153 (18.5)	20 (3.6)	133 (47.8)	94.1% (91.1%–96.4%)	53.8% (47.4%–60.2%)	48.0%
Negative tuberculin skin test	309 (37.4)	144 (26.3)	165 (59.4)	29.1% (22.9%–35.8%)	86.8% (81.2%–91.3%)	15.9%
Elevated ACE	70 (8.5)	9 (1.6)	61 (21.9)	95.8% (92.1%–98.0%)	27.1% (21.4%–33.4%)	22.9%
Elevated lysozyme	50 (6.1)	9 (1.6)	41 (14.7)	91.0% (83.6%–95.8%)	33.6% (25.3%–42.7%)	24.6%

ACE = angiotensin-converting enzyme; BHL = bilateral hilar lymphadenopathy; KP = keratic precipitates; PAS = peripheral anterior synechia; SAU = sarcoidosis-associated uveitis.
*Test specificity is calculated based on the rate of negative test results in class 1, and sensitivity is calculated based on the rate of positive test results in class 2.

between the predicted probability and the observed proportion in the test dataset (Fig S2, available at www.ophthalmologyscience.org). We also explored the predictive performance of only ocular signs or only laboratory investigations. All the clinical signs combined achieved an area under the curve of 0.96 (95% CI, 0.96–0.97), whereas the combined laboratory tests exhibited a poorer predicted performance.

We performed a subgroup analysis by fitting LCA models for Japanese participants and participants from other regions separately. In both settings, the 2-class models were determined to be the best fit for our data based on BIC values (Fig 3). Among the Japanese participants, the 2-class model had an entropy of 0.845, which indicated good separation between classes. Conversely, among participants from other regions, the model did not exhibit good separation between classes (entropy of 0.679). Tests such as trabecular meshwork nodules, optic disc nodule(s)/granuloma(s), elevated angiotensin-converting enzyme, and lysozyme had poor sensitivity in $\geq$ 1 regions, mainly because of the sparse data (Table 7).

Since the fit indices of the 3-class model were comparable to the 2-class model, we conducted a sensitivity analysis for the 3-class model. The results showed that class 1 was comprised of 468 participants and exhibited the lowest proportion of ocular signs or abnormal laboratory investigations, making it most compatible as the candidate non-SAU class (Tables S8 and S9, available at www.ophthalmologyscience.org). Class 2 consisted of the fewest participants, with 142 individuals, but demonstrated a higher likelihood of presenting with IWOS-compatible ocular signs or abnormal laboratory investigations. Therefore, we interpreted class 2 as being most compatible as the candidate SAU class. Class 3 was comprised of 216 participants, with percentages of abnormal ocular signs and laboratory test results in this class generally falling between those of class 1 and class 2. Notably, class 3 had the highest number of participants with multiple chorioretinal peripheral lesions, and the sensitivity of elevated lysozyme, alanine transaminase, and lactate dehydrogenase was higher in class 3 compared with class 2. We propose that class 3 could represent a candidate SAU class with less extensive pulmonary involvement and those with exclusively extrapulmonary SAU.

Discussion

In a large, multicenter, international uveitis cohort, we were able to identify a subgroup of participants with clinical characteristics suggestive of SAU by applying a LCA model that incorporated clinical signs and diagnostic tests recommended by the revised IWOS criteria. While the individual ocular signs or tests from the revised IWOS criteria did not exhibit perfect classification performance, particularly with respect to sensitivity, the combination of these signs or tests yielded satisfactory results in classifying the SAU subclasses identified by the 2-class LCA models. When stratifying by region, the LCA model and the tests employed demonstrated better performance among participants from Japan compared with those from other regions. Notably, the 3-class LCA model, which showed comparable fit indices to the 2-class LCA model, identified distinct SAU subclasses including a non-SAU subtype, an SAU subtype with pulmonary involvement, and an SAU with less pulmonary involvement. The SAU with less pulmonary involvement is an intriguing subclass because this class may be most compatible with patients that have extrapulmonary ocular sarcoidosis, patients with clinical features that align with those by IWOS, but do not have any laboratory

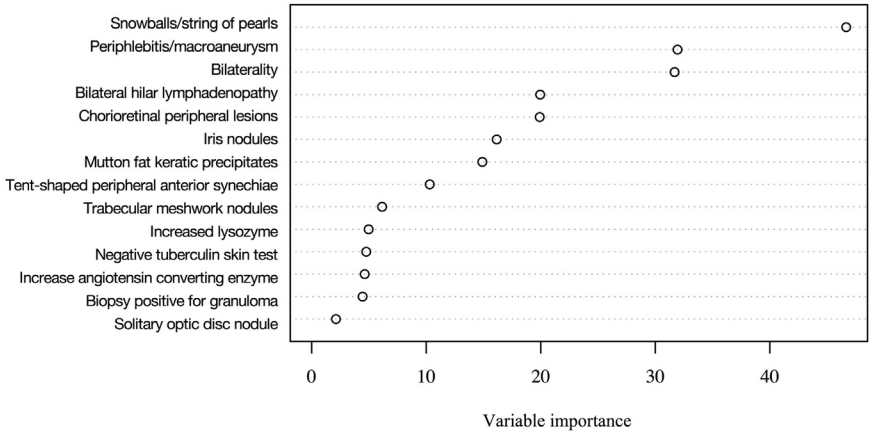

Figure 1. Random forest-based variable importance analysis of tests included in the latent class model with 2 classes for classifying the potent classes.

abnormalities and no pulmonary findings on radiographic imaging. However, it is worth emphasizing that though the class identified through LCA has significant overlap with clinically diagnosed SAU, the features used to identify class membership may not be the same as diagnostic criteria. Nevertheless, LCA results could be suggestive of future improvement in SAU diagnostic criteria.

Approximately half of noninfectious uveitis cases are idiopathic/undifferentiated. However, there are certain ocular clinical exam findings in conjunction with diagnostic tests, such as laboratory and radiographic testing, that may be more compatible with a specific disease. Difficulties may arise when comparing different studies or communicating with patients about exam findings or about their specific diagnosis using imprecise terminology and definitions.[19] The Standardization of Uveitis Nomenclature Project was a major endeavor to codify standardized and universally accepted terminology for 28 major uveitis disease entities.[20] For SAU there were key criteria: (1) a compatible uveitic syndrome (primarily consisting of IWOS clinical signs) of any anatomic class; and (2) evidence of sarcoidosis based on compatible histopathology or radiographic imaging.[21] However, our results indicated that the latent classes were not distinctively separated when using the available ocular signs and tests suggested by the revised IWOS criteria. This may be attributed to the fact that we did not include some essential imaging or biomarker findings, such as positron emission tomography imaging or elevated CD4/CD8 ratio (> 3.5) in BAL fluid, in our LCA model, given that these tests are infrequently used in the diagnosis of uveitis, including in those suspected of having SAU. We did not include biopsy results either since only a small subset of participants underwent tissue biopsies. Secondly, the individual tests in the revised IWOS criteria lack test accuracy for SAU. For example, our random forest analysis identified vitreous snowballs as the most important classifier. However, the determination of whether snowballs are arranged in a string of pearls is subjective, and it is possible for sarcoidosis to feature snowballs that are not in the classically described configuration. Interestingly, bilaterality showed traits contrary to the other tests since it demonstrated favorable sensitivity but inferior specificity. The observed specificity of 58.7% for bilaterality in diagnosing SAU aligns with our hypothesis that approximately 50% of non-SAU cases are unilateral, given that anterior uveitis is the most prevalent anatomic subtype of uveitis and given that infectious anterior uveitis is typically unilateral, whereas autoimmune/autoinflammatory anterior uveitis is typically bilateral.[22–24] Sarcoidosis frequently induces inflammation in both eyes, but bilaterality is not exclusive to SAU as they can be seen

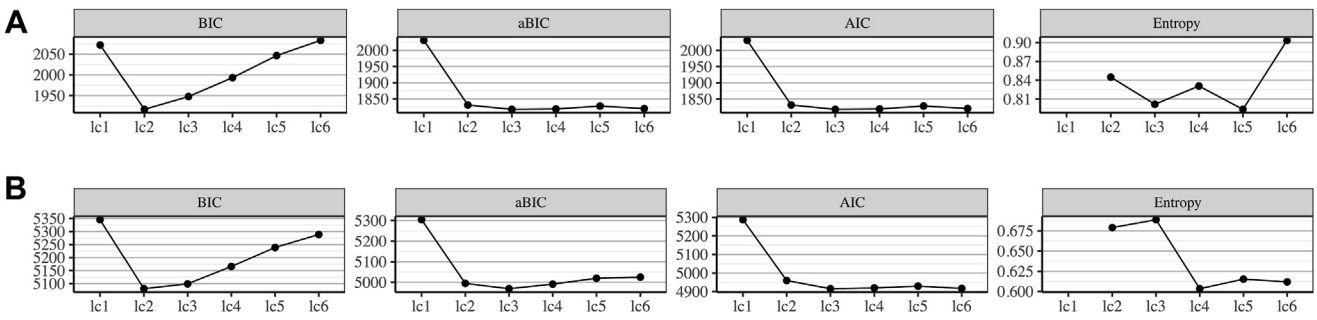

Figure 3. Fit indices for latent class models with prespecified numbers of classes. **A,** Participants from Japan. **B,** Participants from regions other than Japan. aBIC = sample size–adjusted Bayesian information criteria; AIC = Akaike information criteria; BIC = Bayesian information criteria.

Table 7. Sensitivities and Specificities of Individual Tests and Clinical Signs Included in the 2-Class Latent Class Models across Different Regions

Test	Japan			Regions Other than Japan		
	Specificity	*Sensitivity*	*Youden Index*	*Specificity*	*Sensitivity*	*Youden Index*
Mutton-fat KP	85.3% (75.3%–92.4%)	31.3% (22.4%–41.4%)	16.6%	95.9% (93.7%–97.5%)	41.3% (34.1%–48.8%)	37.2%
Iris nodules	96.0% (88.8%–99.2%)	21.6% (13.9%–31.2%)	17.6%	97.2% (95.2%–98.5%)	33.0% (26.2%–40.3%)	30.2%
Trabecular meshwork nodules	100.0% (94.4%–100.0%)	32.5% (22.4%–43.9%)	32.5%	99.7% (98.5%–100.0%)	3.4% (0.9%–8.5%)	3.1%
Tent-shaped PAS	81.2% (69.5%–89.9%)	54.5% (43.6%–65.2%)	35.8%	98.1% (96.2%–99.2%)	16.7% (10.6%–24.3%)	14.8%
Snowball/string of pearls vitreous opacities	97.3% (90.7%–99.7%)	64.3% (54%–73.7%)	61.6%	95.4% (93.1%–97.1%)	55.7% (48.0%–63.3%)	51.2%
Multiple chorioretinal peripheral lesions	94.7% (86.9%–98.5%)	54.2% (43.7%–64.4%)	48.8%	88.2% (84.9%–91.0%)	45.5% (37.9%–53.1%)	33.7%
Periphlebitis and/or macroaneurysm	96.0% (88.8%–99.2%)	59.8% (49.3%–69.6%)	55.8%	96.7% (94.7%–98.2%)	36.2% (29.1%–43.7%)	32.9%
Optic disc nodule(s) and/or solitary choroidal nodule	96.0% (88.8%–99.2%)	2.1% (0.3%–7.3%)	-1.9%	97.6% (95.8%–98.8%)	7.8% (4.3%–12.8%)	5.4%
Bilaterality	60.0% (48.0%–71.1%)	89.9% (82.2%–95.0%)	49.9%	58.7% (54.1%–63.3%)	90.6% (85.3%–94.4%)	49.3%
Abnormal BHL	100.0% (94.8%–100.0%)	63.8% (53.3%–73.5%)	63.8%	91.8% (87.9%–94.8%)	45.5% (37.5%–53.7%)	37.3%
Negative tuberculin skin test	67.7% (48.6%–83.3%)	77.8% (66.4%–86.7%)	45.5%	23.4% (17.2%–30.5%)	93.5% (87.6%–97.2%)	16.8%
Elevated ACE	98.4% (91.2%–100.0%)	0.0% (0.0%–3.9%)	-1.6%	94.8% (90.0%–97.7%)	46.9% (38.1%–55.9%)	41.7%
Elevated lysozyme	100.0% (93.2%–100.0%)	7.9% (2.6%–17.6%)	7.9%	77.6% (63.4%–88.2%)	58.6% (44.9%–71.4%)	36.2%

ACE = angiotensin-converting enzyme; BHL = bilateral hilar lymphadenopathy; KP = keratic precipitates; PAS = peripheral anterior synechia.

in noninfectious/non-SAU, as well as infectious uveitis. Consequently, an LCA model based primarily on ocular signs may not effectively differentiate SAU classes.

It is worth emphasizing that the IWOS criteria may have been heavily influenced by experts who primarily treat Japanese patients, as ocular involvement in sarcoidosis is more prevalent among this population.[25,26] The sensitivities and specificities of current IWOS criteria in diagnosing SAU were relatively high when validated in Japanese cohorts. However, recent evaluation of the performance of the IWOS criteria in an international cohort revealed that most of the diagnostic tests had low sensitivites.[15,27,28] The finding from our LCA also demonstrated that the IWOS criteria exhibited better performance among Japanese participants. As a result, it may be necessary to appropriately tailor the classification criteria to allow for variations that may be inherent due to different regions and populations.

The diagnosis of SAU is straightforward when there are supportive biopsy results in an individual with compatible uveitis. However, assessment of ocular specimens, either aqueous, vitreous, or, when present, iris nodules/vitreous pearls, is generally not possible given the limited tissue volume and the accompanied invasiveness and complications. Although the presence of BHL along with ocular signs may also be suggestive of SAU, chest computed tomography scans in particular are not routinely performed for uveitis.[29] Additionally, some have noted that BHL identified on radiographic imaging can resolve while the ocular findings persist.[30] In addition, in the revised IWOS criteria, newly added laboratory investigations, including lymphopenia, elevated CD4/CD8 ratio (> 3.5) in BAL fluid, parenchymal lung changes consistent with sarcoidosis as determined by pulmonologists or radiologists, and abnormal label uptake on gallium-67 scintigraphy or 18F-fluorodeoxyglucose positron emission tomography imaging, are rarely used in uveitis clinics. Hence, it is essential to consider the patient's symptoms, signs, and medical history comprehensively, rather than relying solely on individual tests or a specific timeframe, when making a diagnosis. Despite the substantial amount of missing data, LCA demonstrated strong concordance with the revised IWOS criteria, indicating its robust classification performance. Furthermore, exploring novel classification algorithms or employing more sensitive biomarkers may be worth considering for the SAU diagnosis.[31–35] Serum soluble interleukin-2 receptor and Krebs von den Lungen-6 mucin have been proposed for inclusion in the classification criteria due to their high sensitivity and specificity in identifying sarcoidosis.[1,3] Additionally, exploring transcriptome-related biomarkers from the peripheral blood as well as aqueous humor may provide valuable insights into identifying SAU.[31,32,34] A previous study observed elevated levels of the intercellular signaling molecule signal transducer and activator of transcription 1 in peripheral blood, orbital tissue, and the lacrimal gland of patients with sarcoidosis.[33] This parallel gene expression in sarcoidosis-affected tissues can facilitate SAU diagnosis by focusing on genes expression patterns in peripheral blood samples without the need for ocular tissue.

The results of the sensitivity analysis for the 3-class model were enlightening because they identified 3 candidate classes within the cohort: a candidate non-SAU subtype, a candidate SAU subtype with pulmonary

involvement, and a candidate SAU that had less pulmonary involvement. The last subtype is particularly intriguing since 5% to 9% of sarcoidosis patients could have extrapulmonary disease, such as skin, peripheral lymph nodes, liver, etc., without pulmonary involvement.[36,37] Classifying a patient as extrapulmonary SAU can be challenging when there are no apparent signs of pulmonary involvement or laboratory abnormalities that corroborate a systemic source and disease burden. Therefore, the results from the 3-class model emphasize the necessity for reliable tests to diagnose SAU in cases where the pulmonary manifestations are absent. However, the results should be interpreted with caution because LCA is an agnostic, unsupervised analysis, and the designations we assigned are our putative tentative interpretations of the latent classes.

Several limitations in our analysis should be acknowledged. First, since our participants were from tertiary centers and some had undergone biopsy, our study population may have a higher representation of patients with more aggressive forms of uveitis as opposed to mild and moderate forms. However, it is important to emphasize that because the LCA model parameters are conditional on the specific hidden states, the proportion of individuals within these states can vary without affecting validity of the LCA model. Nevertheless, severity of the disease could affect LCA results. Therefore, we explored models with different numbers of potential classes to cover the spectrum of SAU. Given this geographically diverse population, our findings should be generalizable to other cohorts of participants from tertiary centers or with severe uveitis. Additionally, 22.4% of the study participants did not attend the 6-month follow-up, resulting in missing laboratory test data. Therefore, these participants were excluded from our analysis. However, it is worth mentioning that the baseline characteristics of the missing participants were comparable to those who had 6-month follow-up. Second, clinician suspicion drove what tests were performed. Only a small proportion of participants who had systemic symptoms were advised to obtain imaging or histology examinations by their ophthalmologists. For example, histological examination via biopsy of suspected sarcoidosis-related lesions is considered the gold standard for sarcoidosis. Nevertheless, only 16.2% of our participants had biopsy information available, preventing its inclusion in our LCA models. Third, none of the tests used in the LCA models demonstrated strong classification performance. This underscores the need for adopting a holistic consideration of patients' health conditions, rather than relying solely on individual tests or a specific timeframe in clinical practice. Fourth, though entropy was not intended for model selection, the entropies of our models were generally < 0.800, suggesting less clear separation between the potential classes. In addition, BICs of our models were relatively high, which could mainly attribute to the large dataset and the long variable list. Besides, since our participants were from multiple clinical centers, the quality and noise in data may vary by regions. Finally, the application of unsupervised machine learning may further exaggerate the uncertainty in defining SAU subgroups. Notwithstanding such limitations, our analysis has the strength of leveraging data from a large international multicenter cohort of uveitis and having a relatively completed set of ocular and systemic tests compatible with sarcoidosis.

Although at present there are, in general, no disease-specific therapies for noninfectious uveitis (particularly when there is no extraocular involvement), as more targeted immunosuppressive therapies are developed, having a specific diagnosis may become relevant. It is therefore important to continue to identify additional sarcoid-specific biomarkers.

In summary, our results suggest that the LCA model, which includes ocular signs and tests from the revised IWOS criteria, can identify a subset of participants with clinical features compatible with SAU. The combination use of these tests demonstrates favorable performance in classifying the subclasses. In addition, it is important to acknowledge that SAU cases may exhibit varying degree of systemic involvement, and in some cases, pulmonary manifestations may be absent. This highlights the importance in enhancing our understanding of the underlying biology of SAU and improving the classification criteria, for instance, by considering additional SAU subtypes or incorporating novel biomarkers. Moreover, it is essential to ensure that these classification criteria are adaptable to different geographic regions.

Footnotes and Disclosures

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Analysis and interpretation: Xiong, Acharya, Rao, Mochizuki, Lietman, Gonzales

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Abbreviations and Acronyms:
BAL = bronchoalveolar lavage; **BIC** = Bayesian information criteria; **BHL** = bilateral hilar lymphadenopathy; **CI** = confidence interval; **IWOS** = International Workshop on Ocular Sarcoidosis; **LCA** = latent class analysis; **SAU** = sarcoidosis-associated uveitis.

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