Ophthalmol Ther (2023) 12:1045–1055
https://doi.org/10.1007/s40123-023-00654-8

ORIGINAL RESEARCH

Validation of UVEDAI: An Index for Evaluating the Level of Inflammatory Activity in Uveitis

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Received: November 10, 2022 / Accepted: January 11, 2023 / Published online: January 23, 2023

ABSTRACT

Introduction: Uveitis is the inflammation of the middle layer of the eye, the uvea, and is a major cause of blindness. None of the instruments used in clinical practice are, in themselves, sufficient to evaluate the course of uveitis. Therefore, it is necessary to develop instruments enabling standardized measurement of inflammatory activity. We developed a

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composite disease activity index for patients with uveitis known as UVEDAI, which considers the overall activity of the eye. The objective of this study was to validate the composite index of ocular inflammation, UVEDAI.

Methods: A multicenter cross-sectional study involving eight Spanish tertiary hospitals. Sixty-two patients aged ≥ 18 years with acute uveitis were recruited. Participants gave informed consent before participating in the study. A full ophthalmological examination was performed by two ophthalmologists to determine inflammatory activity: one used the UVEDAI score and the other used clinical judgment. The ophthalmologists did not share their findings with each other to avoid introducing bias into the analysis. Construct validity was established by means of factor analysis. The criterion validity of the index was determined using an ordinal multivariate regression model, in which the dependent variable was the degree of uveal inflammation (mild, moderate, or high/severe). Cut-off points were determined for the UVEDAI and for the receiver operating characteristic (ROC) curves.

Results: Sixty-two patients were included. Total variance with the three components accounted for 80.32% of the construct validity. Each of the three components identified one type of eye involvement. The discriminatory capacity of UVEDAI was 0.867 (95% CI 0.778; 0.955 $p < 0.001$) for mild versus moderate–high and 0.946 (95% CI 0.879; 1.000 $p < 0.001$) for high versus mild–moderate.

Conclusions: The variables included in UVEDAI enable ocular inflammatory activity to be described with a high degree of accuracy. The index may be used to evaluate and classify this activity with considerable discriminatory power.

Keywords: Uveitis; Composite index; Ocular inflammation; Construct validity; Criterion validity; UVEDAI

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Key Summary Points

The development of a disease activity index could be a major advance in clinical trials as well as in evaluation of treatment response of patients with uveitis in daily clinical practice.

Our group developed a composite disease activity index for patients with uveitis and the objective of the present study was to validate this index.

The study population was patients diagnosed with uveitis and inflammatory activity at the time of their visit to the clinic.

The index classifies inflammatory activity with high discriminatory power.

INTRODUCTION

Uveitis is defined as the inflammation of the middle layer of the eye, the uvea. Today, however, uveitis is a generic term used to describe a heterogeneous group of diseases characterized by intraocular inflammation [1]. Uveitis is a major cause of loss of visual acuity and blindness in developed countries [2, 3]. Given the large number of diseases that lead to uveitis, the condition is classified mainly according to the anatomic location (anterior, intermediate, posterior, and panuveitis), although disease course and other clinical and morphological parameters also play relevant roles in defining the disease [4]. In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group [5, 6] published a series of recommendations with the aim of standardizing the language used to describe and characterize the disease and define its activity. Of note, uveitis that threatens visual acuity affects the posterior pole (intermediate, posterior, and panuveitis). These three anatomic locations often require similar therapeutic strategies—systemic corticosteroids,

immunosuppressants, and biologic drugs—and are grouped together to enable clinical studies on treatment, even though their etiologies are different [7, 8].

Studies on the treatment of uveitis are subject to a number of limitations: there are few randomized clinical trials (RCTs), most studies are prospective or retrospective based on clinical experience, and while they show the benefits of treatment, it remains difficult to compare results [9]. The use of immunosuppressants to treat uveitis is widely established in specialized daily clinical practice, although in general there is little evidence to support decisions on therapy.

The main difficulties in performing RCTs and studies on treatment in this field are the lack of high-quality outcome measures and the considerable variability with respect to the choice of outcome measures to evaluate improvement, stability, or worsening of ocular inflammatory activity [10, 11]. This variability implies that none of the instruments used are, in themselves, sufficient to evaluate the course of uveitis; therefore, it is necessary to develop instruments that enable standardized measurement of inflammatory activity, taking into account the main and least expensive parameters applied in daily clinical practice.

Vitreous haze, as defined by Nussenblatt [12], is the reference measure of the United States Food and Drug Administration (FDA) for RCTs evaluating posterior uveitis [13], although the most recent RCTs on the treatment of uveitis with biologics used multicomponent indices to evaluate activity and improvement [14, 15]. Consistent with other authors, we believe that RCTs should not be designed based on a single criterion. Therefore, our group developed a composite disease activity index for patients with uveitis known as UVEDAI [16], which takes into account the overall activity of the eye. The objective of the present study was to validate this index by determining psychometric properties such as construct and criterion validity.

METHODS

Design

Multicenter cross-sectional cohort study involving eight multidisciplinary uveitis units (MUUs) in Spanish tertiary hospitals.

Study Population

The study population comprised patients aged $\geq$ 18 years diagnosed with uveitis involving any anatomical location (anterior, intermediate, posterior, and panuveitis) and inflammatory activity at the time of their visit to the clinic. We excluded patients who were in complete remission, those participating in a clinical trial or an associated research project, and those with postsurgical or traumatic uveitis. The recruitment period ran from June to December 2019. The study was performed at the specialized care level of the National Health Service. We invited eight MUUs from National Health Service hospitals to participate. All of the centers had complete ophthalmological examination equipment, as reported elsewhere [16], which included spectral domain optical coherence tomography (OCT) devices.

Ethics Statement

This study involved human participants and was approved by the Hospital Clínico San Carlos Ethics Committee. Title: Validation and Sensitivity to Change of an Ocular Inflammatory Activity Index: UVEDAI. Internal Code: 18/196-O_SP. Sponsor and Funder: Spanish Society of Rheumatology. Participants signed an informed consent form before participating in the study. The study was performed in accordance with the Declaration of Helsinki.

Study Development

The degree of ocular inflammation was evaluated independently by two ophthalmologists without sharing data so as not to bias the analysis of the index. One ophthalmologist

measured inflammatory activity according to daily clinical practice, and the other did so using the UVEDAI score. To minimize variability, the evaluations were conducted by both ophthalmologists during the same visit. In the case of patients with bilateral ocular involvement, the eye selected for the analysis was the most inflamed one.

Operating Definitions and Endpoints

An electronic case report form was designed to collect, in addition to sociodemographic variables (e.g., sex, age, educational level), variables that make up the UVEDAI score (anterior chamber cell grade, macular index, vitreous haze, vasculitis, papillitis, number of chorioretinal lesions, and patient's global evaluation), anatomical location of uveitis, etiological diagnosis, and evaluation of ocular inflammatory activity according to the physician's grading, which were stratified as mild, moderate, or high/severe. The operating definitions for the endpoints have been described elsewhere [16].

To reach the objective of validating the UVEDAI, the sample size was estimated at 60 patients. This number was established based on experts' recommendations who estimated that a sample sized of 50–60 patients is enough to validate an index [17, 18].

Statistical Analysis

Patients were recruited homogeneously and consecutively in the eight MUUs until the sample size was reached. The sample was described, and the distribution of variables was assessed to determine the appropriateness of a parametric analysis. In cases of non-normally distributed variables, the necessary transformations were performed to fit them to Gaussian and/or linear models.

A factor analysis was performed to calculate the construct validity. Given the nature of the variables that make up the UVEDAI (categorical or ordinal), a polychoric correlation matrix was used for entry into the factor analysis [19, 20], since the underlying dimensions thus obtained were much more accurate [21, 22]. Polychoric and tetrachoric correlations (both dichotomous variables) were calculated using FACTOR [23, 24]. Once these matrices were obtained, the corresponding factor analysis was performed; the result was validated using SPSS (IBM SPSS v25). All variables, except for the patient's global evaluation, had at least five categories. The patient's evaluation was analyzed by trying various categorization options: five categories (0–1; 2–3; 4–5; 6–7; $\geq$ 8); four categories (0–2; 3–5; 6–8; $\geq$ 9); and three categories ($<$ 4 and $\geq$ 4; $<$ 5 and $\geq$ 5; $<$ 6 and $\geq$ 6). Of all the configurations tried, acceptable results were only obtained for the four-category configuration. Construct validity was evaluated using the total variance explained by the components derived from the factor analysis; UVEDAI was considered to have construct validity when the total variance explained on extracting the components was greater than 70%. For purposes of construct validity, the ophthalmologists confirmed that the components extracted corresponded to the units intended to be measured with this index and established a concept for each of the components extracted.

To determine the criterion validity of the UVEDAI, we performed an ordinal multivariate logistic regression analysis, taking into account the ordinal nature of the dependent variable [mild, moderate, and high/severe). The multivariate analysis used to develop the UVEDAI score was re-run, and receiver operating characteristic (ROC) curves were constructed to discriminate between mild and moderate and high/severe uveitis. The analysis was performed using SPSS (IBM SPSS v25).

RESULTS

A total of 62 patients were included in the study [28 men (45%) and 34 women (55%)], with a mean age of 47.7 $\pm$ 16.9 years. By diagnosis, 30 (48%) had idiopathic uveitis, 8 (13%) had primary uveitis, 20 (32%) had uveitis associated with systemic disease, and 4 (7%), presented other types of uveitis. By anatomical location, 37 (60%) were anterior, 7 (11%) intermediate, 8 (13%) posterior, and 10 (16%) panuveitis. While a complete examination of both eyes was made

in all cases, the eye selected to determine criterion and construct validity was that with greatest activity, that is the one with the most inflammation [32 right (52%), 30 left (48%)]. Information on the variables involved in the UVEDAI score is presented in Table 1.

Construct Validity

The variables that make up each component, together with their weights, are presented in Table 2. Table 3 presents the number of components extracted and the total variance based on three components, thus explaining 80.32% of the same. Component 1 was identified as anterior chamber involvement, although it includes papillitis, with an inverse correlation (anterior chamber involvement was not detected in patients with papillitis and vice versa). Component 2, posterior pole involvement, included as its most representative variables macular edema, vitreous haze, number of foci of chorioretinal lesions, and vasculitis. Lastly, component 3 includes the patient's global evaluation, thus explaining 80.32% of the variance in the construct.

Criterion Validity

The second ophthalmologist evaluated inflammatory activity in uveitis as mild in 28 cases (45%), moderate in 28 (45%), and high/severe in 6 (10%). Table 4 presents all variables in the UVEDAI used in the logistic regression model and comprising the score that set the cut-offs for classification into three categories of inflammatory activity (mild, moderate, and high/severe).

The ROC curves for comparing mild uveitis with moderate or high/severe uveitis and high/severe with mild or moderate uveitis are shown in Fig. 1. The area under the ROC curve (AUROC) for the first comparison was 0.867 [95% CI 0.778; 0.955 ($p < 0.001$)], with a sensitivity of 53.6% for a 10% false-positive rate. In

Table 1 Factors included in the definition of the UVEDAI index

	Frequency (%)	UVEDAI weight
Anterior chamber cell grade[♯]		
0 +	8 (13)	0.00
1 +	15 (24)	-1.41
2 +	18 (29)	-0.72
3 +	16 (26)	1.09
4 +	4 (8)	3.33
Vitreous haze[♯]		
None	42 (68)	0.00
Mild-moderate (1–2 +)	15 (24)	0.38
Severe (3–4 +)	5 (8)	1.37
Macular edema		
≤ 315 µm	49 (79)	0.00
> 315 µm	13 (21)	1.28
Number of active foci (choroidal-retinal lesions)		
0	51 (87)	0.00
1–5	6 (10)	0.69
6 or more	5 (8)	1.61
Inflammatory vascular sheathing		
No	54 (87)	0.00
Yes	8 (13)	1.49
Papillitis		
No	58 (93)	0.00
Yes	4 (7)	1.40
Patient evaluation*	5.02 ± 2.26	0.21

♯ SUN grading system to assess the degree of inflammation in the anterior chamber and vitreous [5]

*Mean ± SD; The weight of the coefficients of the variables that comprise the index

Based on the study by Pato et al. (2017) for classifying uveitis, we used the weights from Table 1 (UVEDAI weight column). Depending on the value of its sum, UVEDAI, the classification obtained was as follows: UVEDAI ≤ 1.05, mild uveitis; UVEDAI ∈(1.05; 4.86), moderate uveitis; UVEDAI > 4.86, severe uveitis. Therefore, the UVEDAI score can range between −1.41 and 12.58

Table 2 Matrix of weights of the variables for each of the components according to the number of components extracted

Variables	Components		
	C1	C2	C3
Anterior chamber cell grade	−0.924	0.044	0.091
Vitreous haze	−0.012	0.915	0.081
Macular edema	0.443	0.746	0.066
Number of active lesions	0.663	0.537	0.210
Vasculitis	0.204	0.532	0.508
Papillitis	0.877	0.312	0.074
Patient evaluation (0–2; 3–5; 6–8; ≥ 9)	−0.051	0.058	0.961

the case of the second ROC curve, which compared uveitis with high/severe activity versus uveitis with mild–moderate activity, the AUROC was 0.946 [95% CI, 0.879; 1.000 ($p < 0.001$)], with a sensitivity of 83.3% for a 10% false-positive rate.

DISCUSSION

Our results confirm the validation of UVEDAI for verifying the construct and criterion validity in this new study population. UVEDAI is a standardized index that provides a valid measurement of global ocular inflammation.

As for construct validity, factor analysis showed that the variance explained with three components was 80.32%, which is an optimal result [25] if compared with the review by Henson and Roberts [26], in which the mean proportion of variance explained by these factors was 52.03%. Two of the three factors removed for analysis corresponded to one anatomical location of uveitis. Anterior chamber cell grade was the variable with the greatest weight for the factor that defined anterior involvement, consistent with the findings of the SUN group [5] for the parameter used to evaluate this involvement. The other variable with greater weight for this component was papillitis, which was only reported in four patients. The correlation between the two variables was high, although it was an inverse correlation; that is, papillitis was not observed in many cases of anterior involvement or vice versa, as observed in clinical practice, since papillitis affects the optic nerve. The dimensions that correlated with component number 2—posterior pole involvement—were vitreous haze, macular edema, number of chorioretinal lesions, and vasculitis, all of which correctly defined this location [5]. In fact, vitreous haze, which was the variable with the greatest weight, is the measurement recommended by the FDA for evaluation of posterior pole activity in RCTs. Factor 3 incorporated the subjective variable, patient's global evaluation, which is maintained as a relevant item in the index in the same way that it forms part of the other composite indices (DAS28 [27, 28], SDAI and CDAI [29]), which are widely used in the standard examination to evaluate rheumatic disease activity and in RCTs. In our study, each of the variables adequately described each of the three components, and the construct validity was confirmed.

In the absence of a validated gold standard, measurement of criterion validity was not ideal. Similarly, when UVEDAI was applied to the new population, it proved to have good discriminatory and classificatory capacity depending on the degree of inflammatory activity. UVEDAI classified patients with moderate and high activity better than those with mild activity, although both ROC curves showed it to not only have good discriminatory capacity, with values very close to those obtained when it was developed [16], but also the ability to confirm the criterion validity.

The main strength revealed by validation of the present index is its usefulness as a standard tool supported by variables taken from examinations carried out in daily clinical practice, including OCT, without the need for complex diagnostic equipment or invasive tests. Consistent with other experts on validation [30], we believe that the main advantages of composite scores over a set of single measures are avoidance of duplication and greater sensitivity to change. It is noteworthy that UVEDAI, which

Table 3 Total variance explained by the components and by the number of components extracted after Varimax rotation (three components)

Component	Initial eigenvalues			Rotation sums of squared loadings		
	Total	Variance, %	Cumulative, %	Total	Variance, %	Cumulative, %
1	3.350	47.852	47.852	2.304	32.920	32.920
2	1.433	20.473	68.325	2.068	29.544	62.464
3	0.840	11.999	80.324	1.250	17.860	80.324
4	0.629	8.990	89.314			
5	0.451	6.440	95.754			
6	0.223	3.193	98.947			
7	0.074	1.053	100.000			

Table 4 Ordinal logistic regression model of uveitis activity levels (ophthalmologist two), including all variables in UVEDAI

Variables	Estimation	SE	Wald	Sig.	95% Confidence interval	
					Lower limit	Upper limit
Patient evaluation	0.361	0.168	4.604	0.032	0.031	0.691
Chamber = 1 +	−2.212	1.487	2.212	0.137	−5.127	0.703
Chamber = 2 +	−1.471	1.405	1.096	0.295	−4.225	1.283
Chamber = 3 +	−0.830	1.423	0.340	0.560	−3.618	1.959
Chamber = 4 +	0.508	1.743	0.085	0.771	−2.909	3.924
Vitreous haze = mild–moderate	1.662	0.765	4.720	0.030	0.163	3.161
Vitreous haze = intense	4.242	1.783	5.657	0.017	0.746	7.738
Macular edema > 315	2.661	0.999	7.101	0.008	0.704	4.619
Number of lesions = 1–5	−0.859	1.507	0.325	0.569	−3.812	2.095
Number of lesions = 6 or more	1.009	1.463	0.475	0.491	−1.858	3.876
Vasculitis = yes	0.300	1.073	0.078	0.780	−1.803	2.403
Papillitis = yes	−1.135	1.564	0.526	0.468	−4.201	1.931
Constant						
Classification = mild	1.301	1.584	0.674	0.412	−1.804	4.407
Classification = moderate	6.033	1.886	10.233	0.001	2.336	9.729

evaluates global ocular inflammatory activity, not only enables physicians to compare the activity of uveitis independently of the cause, but can also serve as a useful tool for daily patient assessment, evaluation of response to treatment, and performance of future clinical studies and trials with minimal methodological difficulties. Accurate methods that make it

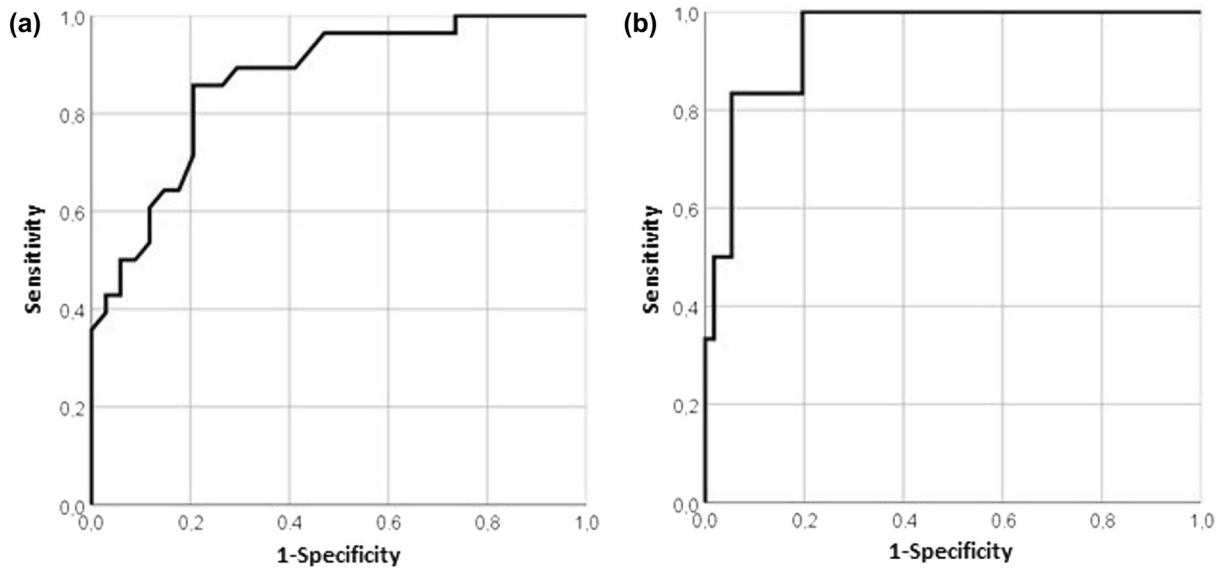

Fig. 1 ROC curves for discriminating between **a** patients with mild uveitis versus moderate–severe uveitis and **b** patients with severe uveitis versus mild–moderate uveitis

possible to evaluate ocular activity in this field must be developed and validated. To our knowledge, no other index that measures this activity has been reported. Another key strength of our study is that, to avoid potential circularity and ensure that the data extracted were reliable, the two ophthalmologists evaluated the patient at the same visit, albeit independently and without sharing the findings of their evaluations.

Our study is limited by the use of the clinical opinion of the ophthalmologist as the gold standard for classifying inflammatory activity. However, as mentioned in the study on the development of UVEDAI [16], our decision was based on the fact that there is currently no reported standard set of criteria to define ocular activity with which we can compare our index. The clinical opinion of the ophthalmologist is habitually used to make clinical and treatment decisions, and some studies define the outcome as an "improvement" in activity according to the physician's opinion [31]. As pointed out above, the physician's opinion has been used in the development of other composite indices, such as the Disease Activity Score (DAS) [32] and DAS28 [28], which are widely used both in clinical practice and in RCTs.

CONCLUSION

The variables included in UVEDAI very accurately describe ocular inflammation. The index also classifies inflammatory activity with high discriminatory power, especially for extreme values. Given that evaluations based on the clinical opinion of the specialist performing the examination are subjective, we believe that having a structured index is highly beneficial when standardizing criteria.

Studies on the interobserver reliability and sensitivity to change of UVEDAI are currently underway to complete its evaluation.

ACKNOWLEDGEMENTS

We would like to thank the following individuals who directly contributed to this study: Enrique González Dávila (who performed the statistical analysis), Zulema Plaza, Félix Francisco, MD and Cruz Fernández Espartero, MD

Funding. We would like to acknowledge the support of Abbvie: this study was conducted with an unrestricted grant from Abbvie. The Spanish Society of Rheumatology is the sponsor

and funder of this study and the journal's Rapid Service Fee, and has participated in the study design; in the analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The corresponding author had full access to all study data and had final responsibility for the decision to submit the manuscript for publication.

Author Contributions. EP, MAMM, LB, LMC, MEO, JSC, MCC, AF, FRG, DDV, SMF and RMF contributed to the protocol and design of the study. EP is principal investigator of this study. EP, LB, LMC, MEO, MCC, AF, TDV, FRG, MSM, SGO, SLS, IGL, IGG, JA, MGA, MTS, AMU, EVP and RMF collected the patient data. MAMM and JSC conducted the data analysis, coordinated the study design process, and implemented the study. MAMM performed and wrote the statistical analysis. EP, MAMM and JSC wrote the manuscript. All authors critically reviewed and approved the final version.

Disclosures. Esperanza Pato-Cour, M[a] Auxiliadora Martin-Martinez, Lara Borrego-Sanz, Lucia Martinez-Costa, Mar Esteban-Ortega, Jesús T Sánchez-Costa, Miguel Cordero-Coma, Alejandro Fonollosa, Teresa Diaz-Valle, Fayna Rodríguez-González, Maite Sainz-de-la-Maza, David Diaz-Valle, Samuel Gonzalez-Ocampo, Sara López-Sierra, Isabel Garcia-Lozano, Irene Garzo-García, Joseba Artaraz, Maria Gurrea-Almela, Marta Tejera, Aina Moll-Udina, Elia Valls-Pascual, Santiago Muñoz-Fernández and Rosalía Méndez-Fernandez have nothing to disclose.

Compliance with Ethics Guidelines. All of the patients gave their written informed consent to participate, and the study was performed according to the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committees.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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