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Development of revised diagnostic criteria for Fuchs' uveitis syndrome in a Chinese population

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ABSTRACT

Background/aims Fuchs' uveitis syndrome (FUS) is one of the frequently misdiagnosed uveitis entities, which is partly due to the absence of internationally recognised diagnostic criteria. This study was performed to develop and evaluate a set of revised diagnostic criteria for FUS.

Methods The clinical data of Chinese patients with FUS and patients with non-FUS were collected and analysed from a tertiary referral centre between April 2008 and December 2020. A total of 593 patients with FUS and 625 patients with non-FUS from northern China were enrolled for the development of diagnostic criteria for FUS. Three hundred and seventy-seven patients with FUS and 503 patients with non-FUS from southern China were used to validate the criteria. Clinical symptoms and ocular signs were collected from all patients with FUS and patients with non-FUS. Multivariate two-step cluster analysis, logistic regression and decision tree algorithms in combination with the clinical judgement of uveitis experts were used to revise diagnostic criteria for FUS.

Results Three essential findings including diffuse iris depigmentation, absence of posterior synechiae, mild inflammation in the anterior chamber at presentation and five associated findings including mostly unilateral involvement, cataract, vitreous opacities, absence of acute symptoms and characteristic iris nodules were used in the development of FUS diagnostic criteria. All essential findings were required for the diagnosis of FUS, and the diagnosis was further strengthened by the presence of associated findings.

Conclusion Revised diagnostic criteria for FUS were developed and validated by analysing data from Chinese patients and showed a high sensitivity (96.55%) and specificity (97.42%).

INTRODUCTION

Fuchs' uveitis syndrome (FUS) is a chronic, mostly unilateral anterior uveitis, accounting for approximately 7% of Chinese patients with uveitis.[1] It is one of the frequently misdiagnosed uveitis entities in the world.[1–4] Patients with FUS generally have an insidious onset and low grade of disease activity, and often present with an asymptomatic mild inflammation.[5 6] One of the important signs of FUS is heterochromia in white races.[7 8] However, this sign is infrequently observed in patients with FUS from a yellow or black population, who have a dense melanin concentration in their iris.[9–11] Although patients with FUS generally have a good prognosis, incorrect diagnosis may lead to unnecessary therapy and accelerate the development of cataract and secondary glaucoma.[12–14] Therefore, a correct diagnosis is absolutely necessary for patients with FUS.

Throughout the history of reporting of FUS, the diagnosis of this syndrome has been a challenge due to its diverse and easily neglected manifestations. Kimura *et al*[15] proposed the classical triad of signs (heterochromia, cyclitis and cataract), based on the clinical data from 750 American patients with uveitis (including 23 patients with FUS). La Hey *et al*[2] made some modifications to the description made by Kimura and described a set of integrated diagnostic criteria which included the predominant clinical findings observed in 51 Dutch patients with FUS. The Standardisation of Uveitis Nomenclature (SUN) working group[16] developed classification criteria for FUS according to the data from 1083 cases of anterior uveitis (including 146 FUS) by machine learning. The criteria stated above, especially the La Hey criteria have been widely used in clinical practice for a long time. However, there are still some potential limitations of these criteria that need further discussion. On the one hand, the three criteria were created from data mostly gathered from white patients. On the other hand, the sample size (23, 51 and 146 patients with FUS) used to develop these criteria was relatively small. Simply using the triad of signs proposed by Kimura is not enough to make a correct diagnosis. With regards to the La Heycriteria, over-emphasis on presenting with all essential findings and at least two associated findings may lead to an under-diagnosis of FUS. The classification criteria by the SUN working group emphasise specificity (exclusion of patients without the disease), which may lead to partial missed diagnoses. In this study, we therefore developed a set of revised diagnostic criteria (RDC) for FUS, based on the data obtained from a large number of Chinese patients and show that the chosen criteria have a high sensitivity and specificity.

METHODS

Data sets

A retrospective study was performed based on the clinical manifestations of 970 patients with FUS and 1128 patients with non-FUS referred to the uveitis centre of the First Affiliated Hospital of Chongqing Medical University during April 2008 to December 2020. The definition of FUS was made according to the La Hey criteria in combination with the clinical judgement of our uveitis specialists. Patients with other uveitis entities (online supplemental table 1[17–20]), who presented with signs and symptoms of anterior uveitis, served as controls. Uveitis caused

Table 1 Patients' characteristics

Variables	Development set			Evaluation set		
	FUS group	Control group	P value	FUS group	Control group	P value
Number	593	625		377	503	
Mean age at disease onset (SD) (range), years	32.3 (11.3) (8–70)	37.9 (14.9) (3–79)	<0.01	34.6 (12.8) (3–84)	41.2 (16.0) (5–86)	<0.01
Mean disease duration (SD) (max), years	3.8 (5.5) (37)	3.2 (5.9) (48)	0.10	3.9 (6.5) (35)	3.1 (6.3) (50)	0.10
Male, No. (%)	270 (45.5)	288 (46.1)	0.85	199 (52.8)	245 (48.7)	0.23
Han ethnicity, No. (%)	573 (96.6)	602 (96.3)	0.77	357 (94.7)	486 (96.6)	0.16
Blurred vision (%)	344 (58.0)	300 (48.0)	<0.01	237 (62.9)	259 (51.5)	<0.01
Decreased vision (%)	328 (55.3)	407 (65.1)	<0.01	181 (48.0)	316 (62.8)	<0.01
Floaters (%)	281 (47.4)	177 (28.3)	<0.01	133 (35.3)	115 (22.9)	<0.01
Eye pain (%)	198 (33.4)	316 (50.6)	<0.01	144 (38.2)	256 (50.9)	<0.01
Redness (%)	171 (28.8)	395 (63.2)	<0.01	108 (28.6)	287 (57.1)	<0.01
Photophobia (%)	153 (25.8)	247 (39.5)	<0.01	90 (23.9)	194 (38.6)	<0.01
Tears (%)	105 (17.7)	180 (28.8)	<0.01	51 (13.5)	134 (26.6)	<0.01
Distorted vision (%)	9 (1.5)	56 (9.0)	<0.01	11 (2.9)	41 (8.2)	<0.01
Unilateral involvement (%)	549 (92.6)	308 (49.3)	<0.01	345 (91.5)	278 (55.3)	<0.01
Mild inflammation in the anterior chamber at presentation (%)	583 (98.3)	252 (40.3)	<0.01	364 (96.6)	195 (38.8)	<0.01
Stellate or medium-sized keratic precipitates (%)	544 (91.7)	77 (12.3)*	<0.01	347 (92.0)	73 (14.5)*	<0.01
Anterior chamber flare (%)	534 (90.1)	392 (62.7)	<0.01	332 (88.1)	304 (60.4)	<0.01
Cells in the anterior chamber (%)	100 (16.9)	213 (34.1)	<0.01	64 (17.0)	146 (29.0)	<0.01
Diffuse iris depigmentation (%)	593 (100.0)	27 (4.3)†	<0.01	377 (100.0)	14 (2.8)†	<0.01
Absence of posterior synechiae (%)	593 (100.0)	411 (65.8)	<0.01	377 (100.0)	348 (69.2)	<0.01
Elevated intraocular pressure (%)	222 (37.4)	237 (37.9)	0.86	132 (35.0)	207 (41.2)	0.06
Iris nodules (%)	69 (11.6)	13 (2.1)	<0.01	39 (10.3)	12 (2.4)	<0.01
Cataract (%)	429 (72.3)	164 (26.2)	<0.01	253 (67.1)	126 (25.0)	<0.01
Vitreous opacities (%)	315 (53.1)	113 (18.1)	<0.01	167 (44.3)	84 (16.7)	<0.01

*Medium-sized keratic precipitates are usually observed in Posner-Schlossman syndrome, and occasionally found in Vogt-Koyanagi-Harada, idiopathic chronic anterior uveitis and presumed virus anterior uveitis.
†Diffuse iris depigmentation with uneven appearance is observed in Posner-Schlossman syndrome.
FUS, Fuchs' uveitis syndrome.

by infectious agents such as tuberculosis, syphilis and AIDS or associated with systemic disease including tubulointerstitial nephritis-associated uveitis syndrome and inflammatory bowel disease were all excluded. The diagnosis of the enrolled patients was made by more than two specialists from referring hospitals and then verified by uveitis specialists from our centre. In view of the potential impact of geographical factors on the diseases profile, we developed the RDC based on patients from northern China and then validated the novel set of criteria on a group of patients referred to us from southern China. The two parts of the country were demarcated by the Yangtze River. All patients were enrolled anonymously.

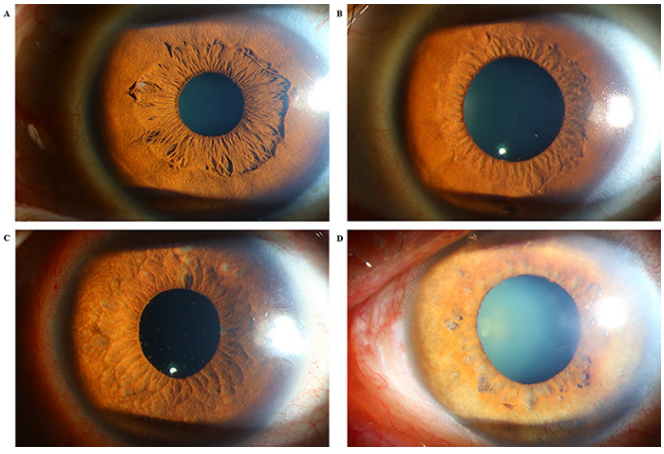

Figure 1 Diffuse iris depigmentation in patients with Fuchs' uveitis syndrome. No iris depigmentation (A), slight iris depigmentation (B), obvious iris depigmentation (C) and striking iris depigmentation (D).

Demographic characteristics and medical history (symptoms and signs) of all patients were collected anonymously at the patients' initial visit, and also included previous clinical records from referring hospitals (table 1).[21] The same uveitis specialist (PY) inquired about the medical history and examined all patients. In our study, elevated intraocular pressure (IOP) was defined as an IOP ≥21 mm Hg. Mild inflammation in the anterior chamber at presentation was defined as the presence of stellate or medium-sized keratic precipitates (KPs) and/or minimal cells and flare in the aqueous (1+ or 2+) at initial visit at our centre or from the clinical records of the referring hospitals.[22] Previous studies reported that the KPs in patients with FUS are characterised by a stellate appearance or a medium size, which are distributed diffusely or centrally.[1 4 23] Diffuse iris depigmentation was defined as a uniform shedding of pigment in the iris. In patients with FUS, slight iris depigmentation usually occurs at the pupillary collar and is accompanied by effacement of the iris crypts. With the gradually increasing loss of pigment, heterochromia (striking iris depigmentation) may eventually occur. Different degrees of diffuse iris depigmentation are shown in figure 1. These changes in the iris are easily detected with a slit-lamp biomicroscope with a narrow slit beam. In normal eyes, a translucent zone is rarely observed and the slit-beam band has a smooth appearance. Whereas in case of iris depigmentation, the transparent zone gradually becomes larger and the slit-beam band becomes curved (figure 2). Iris nodules in patients with

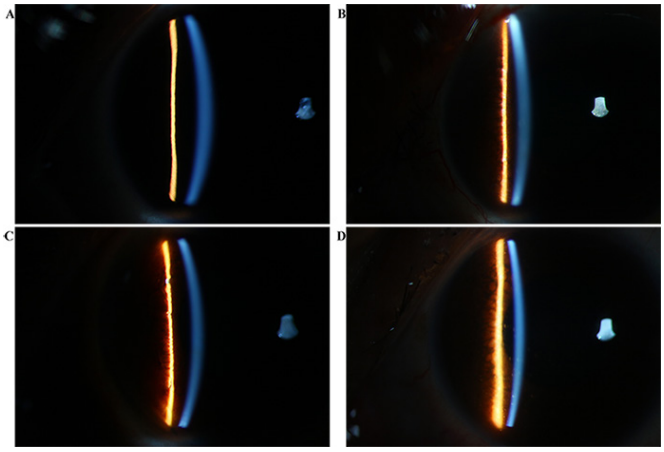

Figure 2 The grade of iris depigmentation in patients with Fuchs' uveitis syndrome. 0: no iris depigmentation (A), I: slight iris depigmentation (B), II: obvious iris depigmentation (C), III: striking iris depigmentation (D).

FUS generally presented as small white nodules at the pupillary margin (Koeppe nodules) or white dots scattered on the anterior surface of the iris (Busacca nodules).[2 24] Koeppe nodules and Busacca nodules observed in FUS are quite different from those observed in granulomatous uveitis (online supplemental figure 1). They are usually smaller in size and definitely show a fluffy appearance.[1 25] Vitreous opacities could be assessed with a slit-lamp biomicroscope or by B-scan ultrasonography.

Developing the RDC for FUS

A total of 593 patients with FUS and 625 patients with non-FUS from northern China were used as a 'development set' for establishing the RDC. Complete clinical data were obtained for each patient and evaluated by using a data mining method (multivariate two-step cluster analysis,[26] binary logistic regression[27] and decision tree[28]) to establish the RDC. Description of the development of the RDC is given in detail in the online supplemental file 1.

Evaluating the RDC for FUS

An evaluation set was used to validate the developed diagnostic efficacy of the RDC for FUS, and included 880 patients with uveitis (377 FUS and 503 non-FUS) from southern China. The sensitivities, specificities and area under the receiver operating characteristic (ROC) curves among the RDC, the La Hey criteria and the SUN classification criteria were compared using this evaluation set.

Statistical analyses

Quantitative variables were compared using the Student's t-test. Categorical variables were recorded as frequencies or percentages and compared with the χ^2 test. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and regression coefficient (B points) of the variables were recruited after binary logistic regression analysis. Sensitivities, specificities and ROC curves with calculations of area under the receiver operating characteristic curves (AUCs) were estimated among the RDC, the La Hey criteria and the SUN classification criteria. AUCs were computed for each finding with 95% CIs by the exact Clopper-Pearson method. SPSS V.24.0 (IBM) was used to analyse all the aforementioned methods. Python scikit-learn package V.0.18.2 was used to conduct decision tree classification. A p value <0.05 was considered significant.

RESULTS

Development of RDC for FUS

In the development set, the data of 593 patients with FUS and 625 control patients from northern China were analysed to develop the RDC for FUS. The demographic data and clinical manifestations in the patients with FUS and control patients are shown in table 1. Almost all patients with FUS showed varying degrees of diffuse iris depigmentation without posterior synechiae. There were significant differences in all variables between the FUS and control groups (p<0.01, table 1) except the mean disease duration, gender distribution, the number of Han Chinese and elevated intraocular pressure. A total of 16 variables with a p<0.01 after using Student's t-test or the χ^2 test were used as candidate factors for the diagnostic model.

The multivariate two-step cluster analysis was used to analyse these 16 candidate variables and identified only two distinct clusters that discriminated patients with FUS (n=610) from patients with non-FUS (n=608). This analysis showed that diffuse iris depigmentation was a significant determinant of phenotype clustering, ranking the highest among the clustering variables. A total of seven variables with 'Importance' >0.05 are showed in online supplemental figure 2). The 16 candidate variables were also analysed by a stepwise binary logistic regression with forward selection. Six variables showed statistical significance (p<0.05). Detailed information (OR, sensitivity, specificity, PPV, NPV, PLR, NLR and regression coefficient) of these six variables is shown in table 2. After analysing the results of cluster analysis and logistic regression, a total of eight variables (diffuse iris depigmentation, mild inflammation in the anterior chamber at presentation, unilateral involvement, cataract, absence of posterior synechiae, redness, vitreous opacities and iris nodules) were chosen to develop the RDC for FUS.

The decision tree model was subsequently developed to explain the relationship between the eight variables and disease

Table 2 Detailed information of variables with p<0.05 in binary logistic regression

Variable	OR	Sensitivity, %	Specificity, %	PPV,%	NPV, %	PLR, %	NLR, %	B points
Diffuse iris depigmentation	–	100.00	95.68	95.65	100.00	23.15	0.00	−64.38
Mild inflammation in the anterior chamber at presentation	86.3	98.31	59.68	69.82	97.39	2.44	0.03	−18.91
Absence of posterior synechiae	–	100.00	34.24	59.06	100.00	1.52	0.00	−44.94
Vitreous opacities	5.13	53.12	81.92	73.60	64.81	2.94	0.57	−30.71
Cataract	7.35	72.34	73.76	72.34	73.76	2.76	0.38	−15.74
Iris nodules	6.20	11.64	97.92	84.15	53.87	5.60	0.90	−31.30

B points, regression coefficient.
NLR, negative likelihood ratio; NPV, negative predicted value; PLR, positive likelihood ratio; PPV, positive predicted value.

Table 3 Diagnostic criteria for Fuchs' uveitis syndrome (FUS) disease

Essential findings	Associated findings
A Diffuse iris depigmentation	A Mostly unilateral involvement
B Absence of posterior synechiae	B Cataract
C Mild inflammation in the anterior chamber at presentation*	C Vitreous opacities
1. Stellate or medium-sized keratic precipitates (stellate appearance or medium size, usually distributed diffusely or centrally)	D Absence of acute symptoms, generally presenting without severe redness
2. Minimal cells and flare in the aqueous (1+ or 2+)	E Characteristic iris nodule†

All essential findings were required for the diagnosis of FUS, and were strengthened by the presence of associated findings.
*Mild inflammation in the anterior chamber at presentation must be determined in accordance with one and/or two at initial visit or from the clinical records obtained from referring hospitals.
†Characteristic iris nodule was defined as small white nodules at the pupillary margin (Koeppe nodules) or white dots scattered on the anterior surface of the iris (Busacca nodules), showing a fluffy appearance.

diagnosis, and was based on recursive partitioning analysis. As shown in online supplemental figure 3, 'diffuse iris depigmentation' was positioned at the top of the tree model, followed by 'mild inflammation in the anterior chamber at presentation' and 'absence of posterior synechiae'. A prediction result was attached to each terminal node. When the input of one of these three variables mentioned above was '0', the prediction result was taken as the output of a terminal node ('Non-FUS'). This decision tree model showed that the presence of these three signs was required for the diagnosis of FUS and included diffuse iris depigmentation, mild inflammation in the anterior chamber at presentation and absence of posterior synechiae. Three variables (unilateral involvement, cataract and vitreous opacities) had no effect on the results of the final classification ('FUS') and were included as associated findings. The other two variables (redness and iris nodules) were not shown in the decision model but may be useful for the prediction of FUS and were also included as associated findings. According to the clinical judgement of uveitis experts, 'redness' could be summarised as absence of acute symptoms, and characteristic iris nodules might be more suitable than iris nodules for FUS. All essential findings were required for the diagnosis of FUS, and the diagnosis was further strengthened by the presence of associated findings. The RDC for FUS can be seen in table 3. The differences among the RDC, the La Hey criteria and the SUN classification criteria are shown in table 4.

Validation of the RDC for FUS

In the validation set, we used patients with FUS (n=377) and control patients with uveitis (n=503) from southern China (online supplemental table 1). Sensitivities, specificities and ROC curves with calculations of AUCs were compared among our RDC, the La Hey criteria and the SUN classification criteria (online supplemental table 2). The sensitivity of the RDC was 96.55%, considerably higher than that seen in the SUN classification criteria and the La Hey criteria (84.08% and 77.72%), which proved that our RDC may be the optimal choice to facilitate the inclusion of FUS. The specificity of our RDC (97.42%) was lower than the SUN classification criteria (99.40%), and the same as the La Hey criteria. The ROC curves of the three criteria are shown in online supplemental figure 4. The AUC of the RDC was 0.970 (95% CI, 0.957 to 0.983), which is the highest among the three criteria, suggesting that our RDC is superior for the diagnosis of FUS in a Chinese population. There were statistical differences ($p<0.01$) between our RDC and the other two criteria.

DISCUSSION

In this study we developed a novel set of simple diagnostic criteria to diagnose FUS in Chinese patients with uveitis. We believe that our criteria may also be used in other ethnic populations with

Table 4 Differences among the revised diagnostic criteria (RDC), the La Hey criteria and the SUN classification criteria for Fuchs' uveitis syndrome

	The RDC*	The SUN classification criteria	The La Hey criteria†
The change of iris	Diffuse iris depigmentation‡	Heterochromia OR Unilateral diffuse iris atrophy	Diffuse iris stromal atrophy‡ Iris posterior pigment epithelium atrophy§ Heterochromia§
Synechiae	Absence of posterior synechiae‡	–	Absence of synechiae‡
Anterior inflammation	Stellate or medium-sized keratic precipitates OR Minimal cells and flare in the aqueous (1+or 2+)‡	Stellate keratic precipitates Anterior chamber cells If vitreous cells are present, anterior chamber inflammation also should be present	Characteristic keratic precipitates and/or minimal cells and flare in the aqueous (1+ or 2+)‡
Symptoms	Absence of acute symptoms, generally presenting without severe redness§	–	Absence of acute symptoms (severe redness, pain and photophobia)‡
Vitreous opacities	Vitreous opacities§	–	Vitreous opacities§
Cataract	Cataract§	–	Subcapsular cataract§
Involvement	Mostly unilateral Involvement§	Unilateral uveitis	Unilaterality of the uveitis§
Iris nodule	Characteristic iris nodule§	–	–
Intraocular pressure	–	–	Elevated intraocular pressure§
Fundus	–	No evidence of active retinitis	Chorioretinal lesions§
Others	–	Neither endotheliitis nor nodular, coin-shaped endothelial lesions	–

*All essential findings were required for the diagnosis of Fuchs' uveitis syndrome, and were strengthened by the presence of associated findings in revised diagnosis criteria.
†All essential findings and at least two associated findings must be present in the La Hey criteria.
‡Essential findings in the criteria.
§Associated findings in the criteria.
SUN, Standardisation of Uveitis Nomenclature.

heavily pigmented irises. One of the main criteria is the observation of a diffuse iris depigmentation, which can be seen by careful examination of the iris with a narrow beam on a slit-lamp biomicroscope. We used novel techniques to develop our revised criteria, which included a combination of cluster analysis, logistic regression and decision tree methods.[2 26 29] The RDC established with these three data mining tools included three essential findings and five associated findings and showed a higher sensitivity and larger AUC in comparison to the SUN classification criteria and the La Hey criteria.[2]

FUS is a phenotypic expression of several probable etiologic causes of inflammation which differentiates it from diseases that have defined etiologies like cytomegalovirus anterior uveitis or other herpesvirus-induced anterior uveitis. Until now, the aetiology and underlying mechanism of FUS are not yet clear. Previous studies have shown that *Toxoplasma gondii* and Rubella virus may be possible agents that are involved in the pathogenesis of FUS, but as yet are not used as a diagnostic criterion.[30 31] The diagnosis of FUS is a clinical one. It is not necessary to perform real time PCR analysis in the diagnosis. However, it is definitely necessary to do PCR and aqueous humour analysis in study of the pathogenesis of this disease if samples can be obtained during cataract surgery.

Clinical diagnostic criteria differ from classification criteria, although both try to reduce misdiagnosis, classification criteria typically emphasise specificity when trade-off is required, whereas diagnostic criteria emphasise sensitivity to ensure inclusion of a homogeneous group of patients with characteristic clinical features.[32] The SUN classification criteria for FUS were proposed in 2020 and performed satisfactorily using an internal data set from the SUN working group.[16] In our cohort, the SUN classification criteria also showed a high specificity, but its sensitivity was significantly lower than our RDC, which may due to an overemphasis on the presentation of unilateral involvement in patients with FUS. Previous studies showed that the number of patients with FUS with binocular involvement accounts for 10%–21% from a yellow or black population.[2 10] Mostly unilateral involvement was included as associated findings in our RDC. In our patients with bilateral involvement, stellate or medium-sized KPs distributed diffusely or centrally, mild anterior chamber inflammation and absence of posterior synechiae in combination with diffuse iris depigmentation were of great important features to make the diagnosis.

There are some similar characteristics between our RDC and the La Hey criteria such as the presence of diffuse iris depigmentation (diffuse iris stromal atrophy) and absence of posterior synechiae. It should be noted that our set of criteria was developed by analysing data from 970 patients with FUS and 1128 controls with uveitis. Some of the La Hey criteria, such as heterochromia was not frequently observed in our set of patients but could be incorporated into a composite set of criteria for non-Chinese individuals. More studies are needed to address this issue. As mentioned above, we would like to stress the analysis of iris depigmentation by observation of the translucent zone generated in the iris by using a slit-lamp biomicroscope with a narrow slit-beam. Other uveitis entities like the Posner-Schlossman syndrome may show diffuse iris depigmentation, but this depigmentation is heterogeneous and uneven. Iris depigmentation can also be detected in patients with herpetic uveitis, but here the depigmentation is approximately sectoral and locally distributed at the lesion site. Therefore, the finding of diffuse iris depigmentation is of great importance and quite specific for the diagnosis of FUS.

Our revised criteria propose the concept of 'mild inflammation in the anterior chamber at presentation' that defined as the presence of mild inflammation at initial visit or from the clinical records of the referring hospitals. In practice, many patients had already been treated with anti-inflammatory drugs by local hospitals and mild inflammation may thus be absent at visit. Therefore, it is extremely important to trace back to the previous clinical records. Vitreous opacities were considered as an important associated finding because they were observed in a vast majority of the patients with FUS.[1 3] Characteristic iris nodules were included in our RDC and this sign emphasised the small size and a fluffy appearance of the nodules. Elevated intraocular pressure was not mentioned in our criteria because this variable lost statistical significance due to the presence of patients with Posner-Schlossman syndrome in our control group. Chorioretinal lesions were also not included in our RDC because this sign was not presented in 104 patients with FUS as previously reported[1] and those enrolled in this study. A further comparison of our RDC with the La Hey criteria and the SUN classification criteria shows that our criteria are simpler and superior, since we have confined the diagnosis to three essential criteria and do mention five associated findings as a support of the diagnosis.

We would like to point some limitations of our study. First of all, our findings were obtained from a group of Chinese patients with uveitis and although we believe that it can be generalised to other heavily iris-pigmented populations, this should of course be verified in non-Chinese patients. Another limitation is the fact that consensus among uveitis specialists on diagnosis is modest at best, with great individual variation in the absence of a 'gold standard' for diagnosis of the disease. Our uveitis specialist's opinion plays a strong and somewhat self-referential role in defining criteria. Further validation of our criteria would need a prospective analysis in consecutive patients with uveitis from other ethnic populations.

In conclusion, we developed RDC for FUS using data from 593 patients with FUS and 625 cases with non-FUS uveitis from northern China and validated the developed criteria using another set of patients with uveitis (377 FUS and 503 non-FUS) from southern China. Higher sensitivity and larger AUC were found in our RDC in comparison to the SUN classification criteria and the La Hey criteria. Further validation of the newly developed criteria would need a prospective analysis in other racial or ethnic populations.

Contributors PY and WZ conceived and designed the study. WZ, ZC, HZ, YZ and ZZ collected the clinical data. WZ and GS analysed and interpreted the data. WZ and ZC wrote the initial draft. PY, WZ, ZC and AK judged data interpretation and edited the manuscript. PY supervised the study. All authors provided a final review and approved the manuscript before submission.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 2020027).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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Supplementary Materials

Supplementary Table 1. Uveitis Entities in the Non-Fuchs' Uveitis Syndrome (Non-FUS) Disease Control Group

Entity	**Number (%)**	
	Development Step	Evaluation Step
Idiopathic chronic anterior uveitis	264 (42.2)	212 (42.1)
Presumed viral anterior uveitis[a]	125 (20.0)	97 (19.3)
Posner-Schlossman syndrome	108 (17.2)	113 (22.4)
Vogt-Koyanagi-Harada[b]	45 (7.2)	29 (5.8)
Behcet's disease	40 (6.4)	20 (4.0)
Sarcoidosis-associated anterior uveitis	31 (5.0)	25 (5.0)
Intermediate uveitis	12 (2.0)	7 (1.4)
Total	625	503

[a] The diagnosis of presumed viral anterior uveitis was performed strictly based on the editorial in 2000[16] and the Chinese study in 2019[17].

[b] The diagnosis of Vogt-Koyanagi-Harada syndrome was made according to both the revised diagnostic criteria in 2001[18] and the Chinese diagnostic criteria in 2018[19].

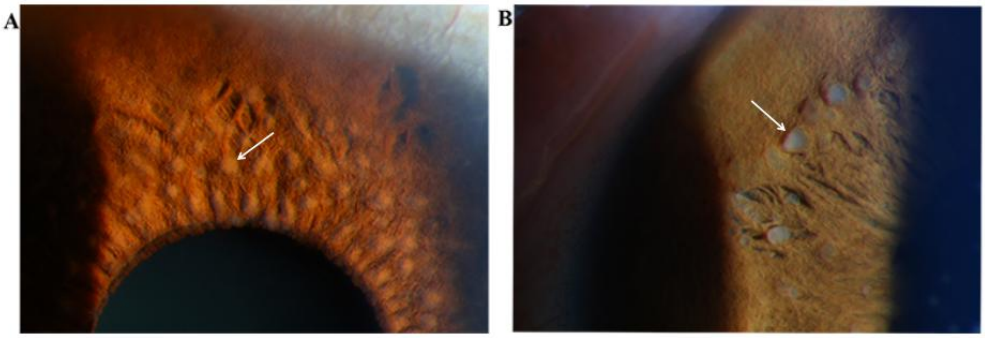
Supplementary Table 2. Performance of the three criteria for Fuchs' uveitis syndrome in the validation set.

	Sensitivity, %	**Specificity, %**	**AUCs** (95%CI)	**P value**[a]
The RDC	96.55	97.42	0.970 (0.957-0.983)	-
the SUN classification criteria	84.08	99.40	0.917 (0.895-0.940)	<0.01
The La Heij criteria	77.72	97.42	0.876 (0.849-0.902)	<0.01

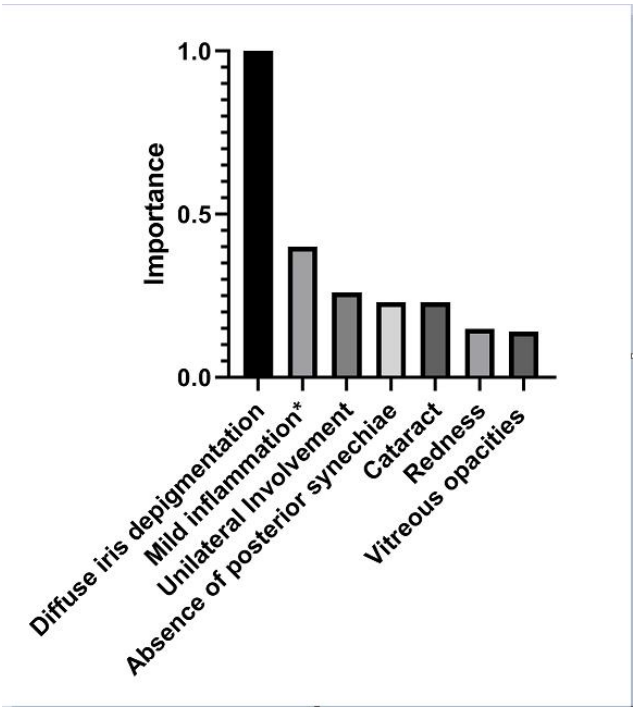
[a]Comparison with the RDC by using McNemar test.

AUCs: area under the receiver operating characteristic curves; RDC: the revised diagnostic criteria; SUN: the Standardization of Uveitis Nomenclature.

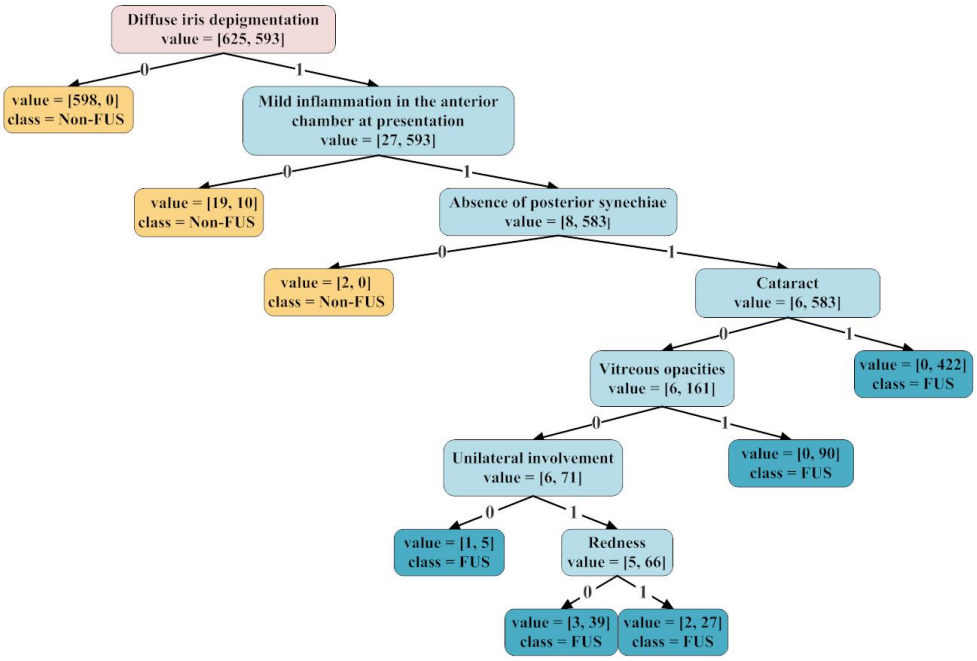
Supplementary Figure



Supplementary Figure 1 Busacca nodules observed in Fuchs' uveitis syndrome
Busacca nodules observed in Fuchs' uveitis syndrome (A) are different from those noted in granulomatous inflammation (B).

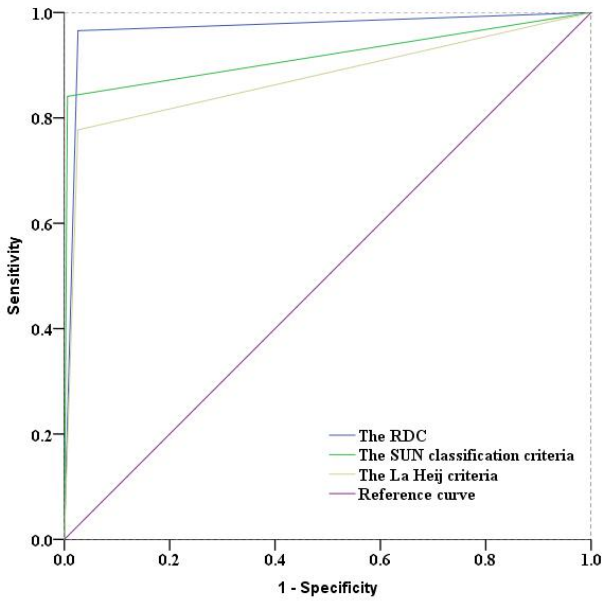


Supplementary Figure 2: The "Importance" >0.05 of nine variables in cluster analysis.
Mild inflammation: Mild inflammation in the anterior chamber at presentation.



Supplementary Figure 3: The decision tree of 8 variables

The decision tree of 8 variables with "Importance" >0.05 in cluster analysis or P<0.05 in logistic regression. "Value" represents the remaining number of the control group and Fuchs' uveitis syndrome group in the development set after segmentation. FUS: Fuchs' uveitis syndrome



Supplementary Figure 4: The receiver operating characteristic curves of the three criteria for Fuchs' uveitis syndrome. The RDC: the revised diagnostic criteria; SUN: Standardization of Uveitis Nomenclature.

Supplementary methods

Three data mining methods

In this study, three data mining methods (multivariate 2-step cluster analysis, binary logistic regression and decision tree) were used to establish the revised diagnostic criteria. In the first step, the Student's t-test and chi-square test were respectively used to compare quantitative and categorical variables between the FUS group and control uveitis group. According to the combined opinions of uveitis experts, some of those variables that had a $p<0.01$ were chosen not only for multivariate 2-step cluster analysis but also for binary logistic regression analysis with a forward selection. Cluster analysis is an exploratory data mining technique, which divides the data into different clusters according to the similarity, so that the patterns in the effective clusters are more similar to each other.[1] Gilbert et al[2] have identified peripheral lesions and intraocular inflammation as distinct clinical phenotypes of multifocal choroiditis and punctate inner choroidopathy by using a cluster analysis approach. In a multivariate 2-step cluster analysis, the optimized Bayesian information criterion was used to determine the number of clusters and a log-likelihood decision rule was used to resolve cluster differentiation. Logistic regression is a powerful method to analyze the relationship between a binary outcome or categorical outcome and multiple influencing factors.[3] A previous study for instance used logistic regression to establish new diagnostic criteria for Takayasu arteritis.[4] The combined use of multivariate 2-step cluster analysis and binary logistic regression analysis was used to screen candidate variables that could be used to develop diagnostic criteria. "Predictor Importance" was calculated and variables with an "Importance" >0.05 in cluster analysis or with a $p<0.05$ in binary logistic regression were used for decision tree classification. The decision tree model was subsequently used to determine the association between the meaningful main effect variables and the disease of interest. Previous studies have shown that "meaningful main effect variables" can be screened by logistic regression and then further used in decision tree models to obtain better results.[5] In the decision trees algorithm, quantitative variables were dichotomized and categorical variables were normalized to "0" or "1" values. By using recursive segmentation analysis between different variables, the decision tree model was built for all potential determinants.[6,7] Each internal node of the decision tree represents a test on a variable, which is related to the final classification results. Each branch represents a test output, and each terminal node represents a class or class distribution. The variable of the root node at the top of the tree model is most important to the classification results.[8] The minimum sample size on the node was set as "50". If the sample size on the node failed to meet this requirement, the segmentation was finished. Based on the decision tree result, each recruited variable was reassessed by uveitis experts and statisticians, leading to the development of a final set of diagnostic criteria. The use of three data mining methods further added to the degree of reliability of the RDC for FUS.

Supplementary Discussion

Clinical differentiation of FUS

As one of the frequently misdiagnosed uveitis entities in the world, FUS is in urgent

need for differentiation from other types of uveitis presenting as chronic anterior inflammation, complicated cataract and elevated IOP. In the control group we included several diseases that need to be differentiated from FUS. For example, patients with idiopathic chronic anterior uveitis, who may present with dust-like KPs and uneven iris depigmentation, may be misdiagnosed as FUS. Patients with idiopathic chronic anterior uveitis however often show bilateral involvement and posterior synechiae. In addition, presumed viral anterior uveitis and Posner-Schlossman syndrome with iris depigmentation are also easily confused with FUS. A few patients with Vogt-Koyanagi-Harada (VKH) disease and Behcet's disease were included in our study. The granulomatous Koeppe nodules and Busacca nodules seen in VKH or sarcoidosis also need to be distinguished from the characteristic iris nodules observed in FUS (Figure 1). In the context of these uveitis types as a control group, we hope that our new set of diagnostic criteria may facilitate the correct clinical identification of FUS.

The complications of FUS

The ocular examinations that focus on slit-lamp biomicroscopy for the bilateral anterior segment of the eye to detect iris abnormalities and the degree of inflammation in the anterior chamber were of great importance for FUS patients. A late diagnosis of FUS may lead to an inappropriate medication resulting in serious complications such as cataract and ocular hypertension. Cataract is often the major cause of visual acuity loss and it is thought that this may be hastened by prolonged use of corticosteroids, although this has not yet been formally proven by randomized clinical trials.[9] The importance of diagnosing FUS is especially important in the light of the fact that these patients may develop glaucoma and regular follow-up is necessary for the timely evaluation of IOP changes. Approximately 40% of FUS patients showed an elevated intraocular pressure in our study. Previous studies showed that the development of secondary glaucoma in FUS patients is variable, ranging between 6.3% and 59% of cases.[10,11] Secondary glaucoma can be controlled by topical and systemic anti-glaucoma medication combined with regular monitoring. Taken together, we recommend that patients have a follow-up visit every 3-4 months in order to detect complications such as cataract and glaucoma, unless they suffer from an exacerbation that may require immediate treatment.

The treatment for FUS patients in our uveitis center

For FUS patients, a detailed history taking, including general information, complaints and associated systemic diseases, were collected at the patients' initial visit in our uveitis center. The best-corrected visual acuity (BCVA) and IOP were obtained on the same day. The ocular examinations focus on slit-lamp biomicroscopy for the bilateral anterior segment of the eye to detect iris abnormalities and the degree of inflammation in the anterior chamber. The correct diagnosis was strengthened by the presence of diffuse iris depigmentation. The cornea, the chamber angle and the anterior vitreous could be evaluated by ultrasound biomicroscopy (UBM) in some FUS patients with elevated IOP. In FUS patients, corticosteroid therapy is often not successful and visual acuity may only improve slightly by this treatment. Generally, a short treatment with topical corticosteroids might be indicated if obvious anterior chamber inflammation is present.

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