Classification Criteria for Cytomegalovirus Retinitis

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

• PURPOSE: **The purpose of this study was to determine classification criteria for cytomegalovirus (CMV) retinitis.**

• DESIGN: **Machine learning of cases with CMV retinitis and 4 other infectious posterior/ panuveitides.**

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

• RESULTS: **A total of 803 cases of infectious posterior/panuveitides, including 211 cases of CMV retinitis, were evaluated by machine learning. Key criteria for CMV retinitis included: 1) necrotizing retinitis with indistinct borders due to numerous small satellites; 2) evidence of immune compromise; and either 3) a characteristic clinical appearance, or 4) positive polymerase chain reaction assay results for CMV from an intraocular specimen. Characteristic appearances for CMV retinitis included: 1) wedge-shaped area of retinitis; 2) hemorrhagic retinitis; or 3) granular retinitis. Overall accuracy for infectious posterior/panuveitides was 92.1% in the training set and 93.3% (95% confidence interval: 88.2-96.3) in the validation set. The misclassification rates for CMV retinitis were 6.9% in the training set and 6.3% in the validation set.**

• CONCLUSIONS: **The criteria for CMV retinitis had a low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 245–254. © 2021 Elsevier Inc. All rights reserved.)**

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Prior to the onset of the acquired immunodeficiency syndrome (AIDS) epidemic, cytomegalovirus (CMV) was a rare disease seen primarily in patients undergoing organ transplants, with estimated frequencies of ~1% for renal transplants and ~0.5% for bone marrow transplants. The primary risk factor for CMV disease was a CMV serum antibody-positive ("seropositive") donor organ transplanted into a CMV-seronegative recipient.[1] With the onset of the AIDS epidemic, CMV retinitis became substantially more common, and prior to the widespread use of modern combination antiretroviral therapy (ART) in the mid-1990s, CMV retinitis was among the most common intraocular infections seen in major urban medical centers in the United States and other developed countries.[1,2] CMV retinitis is an AIDS-defining opportunistic infection. In that era, the lifetime risk of developing CMV retinitis after the onset of AIDS was estimated at 30%.[3] The primary risk factor was a low $CD4^+$ T-cell count, with a substantial majority of cases occurring among patients with $CD4^+$ T-cell counts $\leq$50 cells/μL,[1–3] as CMV-seropositive rates among persons at high risk for human immunodeficiency virus (HIV) infection typically were >90%.[1] With the widespread use of modern ART, the incidence of CMV retinitis among patients with AIDS has decreased by >95%,[1,4] primarily due to immune recovery

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FIGURE 1. Fundus photograph of a case of cytomegalovirus retinitis with a "hemorrhagic" appearance involving the posterior pole, characterized by retinal necrosis and edema, intraretinal hemorrhage and "satellite lesions" at the border.

from or prevention of these levels of immunodeficiency and the attendant restoration of immunity to CMV.[1,5]

Cytomegalovirus retinitis occurs in the context of a systemic infection, and CMV can be detected in the blood of most patients with CMV retinitis, either by culture or polymerase chain reaction (PCR) assay of CMV from a blood specimen.[6,7] When blood and intraocular specimens from an individual are compared at the time of diagnosis of the retinitis using sequencing of the CMV *UL97* gene, there is almost perfect agreement between the 2 isolates.[8] The presumed pathogenesis of CMV retinitis among patients with AIDS is reactivation of latent infection in the context of immunodeficiency, hematologic dissemination to the retina, infection of retinal vascular endothelium, infection of adjacent retina, and unless treated with anti-CMV drugs, spread across the retina.[1,9] The end result of CMV retinitis is full-thickness retinal necrosis, leaving a thin, atrophic, and gliotic scar. Retinal detachments were a common complication of CMV retinitis, often due to multiple retinal tears at the border of normal retina and the atrophic scar. The incidence of retinal detachment is related to the extent of retina involved by CMV retinitis,[1,2] and its incidence has declined in the era of modern ART.[10] Two clinical morphologic variants of CMV retinitis were described: 1) fulminant or hemorrhagic and 2) granular. The hemorrhagic variant presented with a more extensive area of retinal edema and necrosis, admixed with hemorrhage (Figure 1), whereas the granular variant had a "granular" appearance (Figure 2). The fulminant or hemorrhagic variant has been described as having a "pizza pie" or a "cottage cheese and ketchup" appearance. The only difference observed between the 2 variants was the location of the lesions: the hemorrhagic variant occurred more often in the posterior pole, whereas the granular variant occurred more often in the periphery.[1]

Treatments for CMV retinitis approved by the United States Food and Drug Administration have included intravenous ganciclovir; intravenous foscarnet; intravenous cidofovir; valganciclovir (an oral pro-drug of ganciclovir with good oral bioavailability); the sustained-release intraocular ganciclovir implant; and fomivirsen (an intravitreally administered "anti-sense" drug). With the decline in the incidence of CMV retinitis, production of the ganciclovir implant and of fomivirsen were discontinued.[1,11–17] Intravitreal injections of either ganciclovir or foscarnet have been administered as treatments for CMV retinitis.[1,18] However, because of the systemic nature of the CMV infection, absent immune recovery from ART, treatment with intraocular therapy alone is associated with in increased risk of second eye CMV retinitis (among those presenting with unilateral retinitis), visceral CMV disease, and mortality, outcomes still seen the era of modern ART.[1,18] Many patients (especially those with lesions threatening the fovea or optic nerve) in developed countries are treated with an initial series of intravitreal injections of either ganciclovir or foscarnet combined with systemic therapy (eg, valganciclovir). With immune recovery from ART, patients with AIDS can recover immunity to CMV and are able to discontinue anti-CMV therapy.[5,19] The United States Department of Health and Human Services guidelines include the recommendation to stop anti-CMV therapy when CMV retinitis is in-

FIGURE 2. Fundus photograph of a case of cytomegalovirus retinitis involving the periphery, characterized by a "granular" appearance and without hemorrhage.

active and $CD4^+$ T cells have risen to >100 cells/μL for at least 3-6 months. Cohort studies suggest that discontinuation in this circumstance typically can be done safely.[19] The reason for the delay after a rise in $CD4^+$ T cells is that the recovery of immunity to CMV lags the rise in $CD4^+$ T cells by 3-6 months.[5] The rare occurrence of patients with recovered $CD4^+$ T cells but failure to restore immunity to CMV and ongoing problems with recurrent CMV retinitis underscores the importance of immunity specific to CMV for its control.[20]

Patients with CMV retinitis typically have relatively mild amounts of anterior chamber and vitreous inflammation at presentation (reported median vitreous cells grade ½+ and median vitreous haze grade 0+), presumably due to the failure to mount an effective immune response to CMV, and nearly ~90% will have grade 0 vitritis after treatment with anti-CMV agents.[21,22] However, with immune recovery due to ART, the new onset of or an increase in anterior chamber or vitreous inflammation or both can occur, a phenomenon termed immune recovery uveitis (IRU).[22,23] Patients with a diagnosis of CMV retinitis after the initiation of ART may have greater levels of anterior chamber and vitreous inflammation than those diagnosed before the initiation of ART as a consequence of IRU.

Even though much of the information on CMV retinitis comes from patients with AIDS, patients with other forms of immunosuppression, such as those undergoing organ transplants and chemotherapy, may develop CMV retinitis.[24] Rare cases have been reported after intravitreal corticosteroid injection or sustained-release corticosteroid implantation, presumably resulting from local, ocular immune compromise.[25,26] Cases of CMV retinitis occurring in patients with other types of immune compromise appear to behave similarly to cases of CMV retinitis occurring among patients with AIDS in the modern ART era, including the occurrence of IRU when immunosuppression is reduced or discontinued.[24]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration, which has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was CMV retinitis.[27–33]

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[28–32]

• **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and a standardized, menu-driven hierarchical case collection instrument.[29]

• **CASE COLLECTION AND CASE SELECTION:** De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease as previously described.[31,32] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying

articles.[31,32] Because the goal was to develop classification criteria,[33] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[31,32]

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of the cases) and a validation set (~15% of the cases) for each disease, as described in the accompanying article.[32] Machine learning was used in the training set to determine criteria that minimized misclassification. The criteria then were tested in the validation set. For both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm compared to the consensus diagnosis. For infectious posterior and panuveitides, the diseases against which CMV retinitis was evaluated were: acute retinal necrosis (ARN), syphilitic uveitis, tubercular uveitis, and toxoplasmic retinitis.

• **COMPARISON BETWEEN CASES WITH AIDS AND THOSE WITH OTHER IMMUNITY-COMPROMISED CONDITIONS:** Cases with AIDS were compared to cases with other types of immune compromise (eg, organ transplant, chemotherapy). For categorical variables, a comparison was performed using the χ^2 test or the Fisher exact test when the count of a variable was less than 5. Continuous variables were summarized as medians and compared using the Wilcoxon rank sum test. For characteristics with multiple categorical grades, values above and below the median were compared. *P* values are nominal and 2-sided.

RESULTS

A total of 251 cases of CMV retinitis were collected, and 211 (84%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. Those cases of CMV retinitis were compared to cases of infectious posterior/panuveitides, including 186 cases of ARN, 174 cases of toxoplasmic retinitis, 35 cases of syphilitic posterior uveitis, and 197 cases of tubercular posterior or pan-uveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[32] The characteristics of cases with CMV retinitis are listed in Table 1. The comparison between cases with AIDS and those with other forms of immune compromise is listed in Table 2. The comparison between cases with AIDS and cases with other forms of immune compromise revealed demographic differences consistent with those of the AIDS epidemic in the United States, and a statistically significant but clinically modest difference in presenting intraocular pressure (median: 13 mm Hg for cases with AIDS; and 15 mm Hg for cases

TABLE 1. Characteristics of Cases With Cytomegalovirus Retinitis.

Characteristic	Result
Number cases	211
Demographics	
Median IQR (25th 75th) age, y	40 (33, 47)
Men, %	71
Women, %	29
Race/ethnicity, %	
White, non-Hispanic	49
Black, non-Hispanic	18
Hispanic	8
Asian, Pacific Islander	9
Other	15
Missing	1
Uveitis history	
Uveitis course, %	
Acute, monophasic	54
Acute, recurrent	3
Chronic	36
Indeterminate	7
Laterality, %	
Unilateral	64
Unilateral, alternating	0
Bilateral	36
Ophthalmic examination	
Keratic precipitates, %	
None	64
Fine	29
Round	2
Stellate	2
Mutton-fat	2
Other	0
Anterior chamber cells, %	
Grade 0	45
½+	26
1+	17
2+	10
3+	2
4+	1
Anterior chamber flare, %	
Grade 0	70
1+	26
2+	4
3+	0
4+	0
Iris, %	
Normal	96
Posterior synechiae	4
Iris nodules	0
Iris atrophy (sectoral, patchy, or diffuse)	0
Heterochromia	0
IOP, involved eyes	
Median IQR (25th, 75th) mm Hg	13 (12, 16)
Proportion patients with IOP >24 mm Hg in either eye, %	2

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TABLE 1. (*continued*)

Characteristic	Result
Vitreous cells, %	
Grade 0	30
½+	20
1+	31
2+	16
3+	3
4+	0
Vitreous haze, %	
Grade 0	55
½+	14
1+	21
2+	7
3+	2
4+	0
Retinitis characteristics	
Number of lesions, %	
Unifocal (1 lesion)	23
Paucifocal (2–4 distinct lesions)	69
Multifocal (≥5 distinct lesions)	8
Lesion shape, %	
Round or ovoid	11
Placoid or ameboid	35
Wedge-shaped	31
Missing	23
Lesion character, %	
Circumferential	4
Confluent	28
Granular	36
Lesion location, %	
Posterior pole involved	38
Mid-periphery and periphery only	62
Lesion size, %	
<250 μm	5
250–500 μm	10
>500 μm	85
Other features, %	
Retinal vascular sheathing	36
Retinal hemorrhage	61
Systemic disease	
Immunocompromised patients, %	
AIDS	76
Organ transplant	3
Chemotherapy or other immunosuppression	16
Missing	5
Laboratory data, %	
Aqueous or vitreous specimen, PCR-positive for cytomegalovirus	34

IOP = intraocular pressure; IQR = interquartile range; PCR = polymerase chain reaction.

A total of 71 of 71 cases (100%) tested positive for cytomegalovirus.

without). In addition, cases with AIDS had less vitritis (median vitreous haze grade 0) than did cases without AIDS (median vitreous haze grade ½+), but the difference was modest. The classification criteria developed after machine learning are listed in Table 3. Key features of the criteria included necrotizing retinitis with indistinct borders (satellites), immune compromise, and either evidence of intraocular CMV infection (eg, PCR assay results), or a characteristic clinical picture. Features of a characteristic clinical picture for CMV retinitis included a hemorrhagic (Figure 1), granular appearance (Figure 2), or wedge-shaped (Figure 3) retinitis with no to mild vitritis. The overall accuracy for infectious posterior/panuveitides was 92.1% in the training set and 93.3% (95% confidence interval: 88.2-96.3%) in the validation set. The misclassification rate for CMV retinitis in the training set was 6.9% and 6.3% in the validation set. The diseases with which CMV retinitis was most often confused (ie, misclassified) in the training set were toxoplasmic retinitis and syphilitic retinitis and toxoplasmic retinitis and ARN in the validation set.

DISCUSSION

Necrotizing retinitides are characterized by full-thickness retinal necrosis with or without inflammation, which, upon resolution, leave an atrophic and gliotic scar in the involved areas. Clinically, the initial presentation is white to yellow retinal edema and opacity with or without hemorrhage. Necrotizing retinitides may have relatively well-demarcated borders, as in the case of ARN, or have satellites extending into adjacent retina, as seen in CMV retinitis. The classification criteria developed by the SUN Working Group for CMV retinitis have a low misclassification rate, indicating good discriminatory performance against other infectious posterior and panuveitides.[32] Because of the similarities in clinical presentation between cases with AIDS and those with other forms of immune compromise, these criteria appear to be applicable to both situations. The goal of the SUN project was disease classification at presentation, so that cases of active CMV retinitis were submitted and the criteria are most applicable to active retinitis. Atrophic scars from retinitis may be non-specific, and it may be difficult to determine the original cause of such scars.

The diseases with which CMV retinitis was most often confused were 2 other necrotizing retinitides, ARN, and toxoplasmic retinitis. In immunocompromised hosts, toxoplasmic retinitis occasionally may present as a more extensive retinitis without adjacent scars and may be difficult to distinguish from CMV retinitis.[34] In those cases, sampling intraocular fluids using PCR analysis for viruses and *Toxoplasma gondii* organisms may be needed. Rarely, patients with immune compromise (eg, AIDS with low $CD4^+$ T cells) may be infected with 2 or more intraocular pathogens,[2] and the PCR result may be positive for CMV

TABLE 2. Comparison of Cases of Cytomegalovirus Retinitis between Cases with the Acquired Immunodeficiency Syndrome and Cases with Other Immune Compromise

Characteristic	Cases With AIDS	Cases Without AIDS	*P* Value
Number cases	160	51	
Demographics			
Median IQR (25th 75th) age, y	39 (33, 44)	48 (32, 66)	0.02
Men, %	71	71	1
Women, %	29	29	1
Race/ethnicity, %			<0.001
White, non-Hispanic	42	71	
Black, non-Hispanic	23	4	
Hispanic	10	0	
Asian, Pacific Islander	8	12	
Other	16	13	
Missing	1	0	
Uveitis history			
Uveitis course, %			0.09
Acute, monophasic	47	45	
Acute, recurrent	7	4	
Chronic	35	27	
Indeterminate	11	24	
Laterality, %			0.27
Unilateral	65	67	
Bilateral	35	33	
Ophthalmic examination			
Keratic precipitates, %			0.64
None	66	59	
Fine	28	31	
Other	6	10	
Anterior chamber cells, %			0.41
Grade 0	44	45	
½+	28	18	
≥1+	28	37	
Anterior chamber flare, %			0.17
Grade 0	73	63	
1+	22	35	
2+	5	2	
Iris, %			0.38
Normal	96	94	
Posterior synechiae	4	6	
IOP-involved eyes			
Median IQR (25th, 75th) mm Hg	13 (11, 15)	15 (13, 19)	<0.001
Percentage of patients with IOP >24 mm Hg in either eye	0	10	0.001
Vitreous cells, %			0.52
Grade 0	32	25	
½+	21	18	
≥1+	48	57	
Vitreous haze, %			0.01
Grade 0	61	37	
½+	12	22	
≥1+	27	41	
Retinitis characteristics			
Number of lesions, %			0.90
Unifocal (1 lesion)	21	24	
Paucifocal (2–4 distinct lesions)	70	69	
Multifocal (≥5 distinct lesions)	9	7	

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TABLE 2. (*continued*)

Characteristic	Cases With AIDS	Cases Without AIDS	*P* Value
Lesion shape, %			0.17
Round or ovoid	13	8	
Placoid	29	31	
Wedge-shaped	31	33	
Lesion character, %			
Circumferential or confluent	34	29	0.38
Hemorrhagic	59	63	0.40
Granular	37	33	0.39
Lesion location, %			0.06
Posterior pole involved	39	35	
Mid-periphery and periphery only	61	65	
Lesion size, %			0.72
$<$250 μm	5	2	
250–500 μm	8	17	
$>$500 μm	87	81	
Other features, %			
Retinal vascular sheathing	37	33	0.39
Systemic disease			
Laboratory data, %			
Ocular fluid specimen PCR-positive for CMV	24	65	

CMV = cytomegalovirus; IOP = intraocular pressure; PCR = polymerase chain reaction;

A total of 38 of 38 specimens (100%) from tested cases with AIDS were PCR-positive for CMV; and 33 of 33 specimens (100%) from tested cases without AIDS were PCR-positive for CMV.

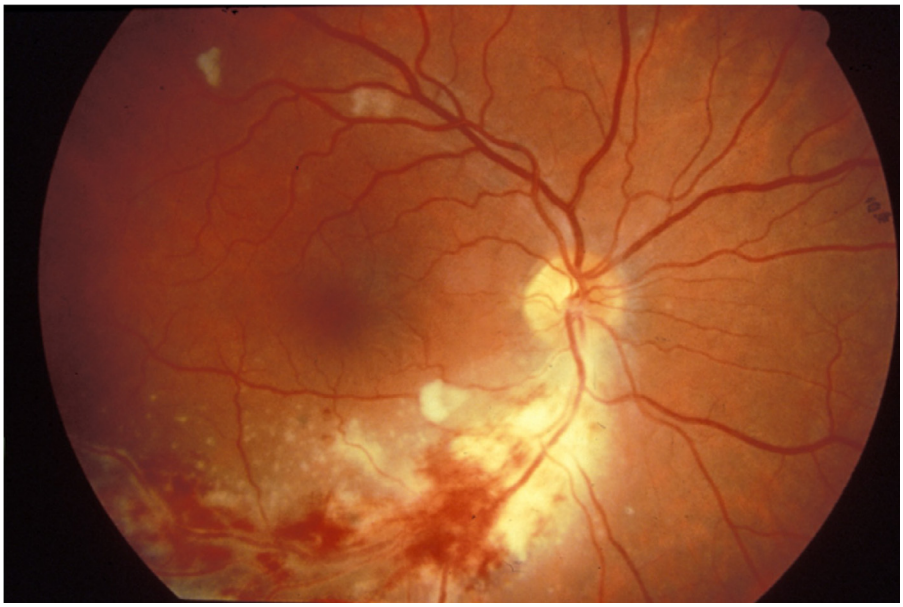

FIGURE 3. Fundus photograph of a case of cytomegalovirus retinitis with a wedge-shaped appearance with the apex "pointing" toward the optic disc.

TABLE 3. Classification Criteria for Cytomegalovirus Retinitis.

Criteria (requires #1 and #2 and either #3 or #4)
1. Necrotizing retinitis with indistinct borders due to numerous small (<50 μm) satellites
AND
2. Immune compromise, either
a. Systemic (eg, AIDS, organ transplant, chemotherapy) OR
b. Ocular (eg, intraocular corticosteroids or chemotherapy)
AND (#3 or #4)
3. Characteristic clinical picture ([a or b or c] And d)
a. Wedge-shaped area of retinitis OR
b. Hemorrhagic appearance of the retinitis OR
c. Granular appearance of the retinitis AND
d. Absent to mild vitritis
OR
4. Evidence of intraocular infection with cytomegalovirus
a. Positive PCR for cytomegalovirus from either the aqueous or vitreous specimen
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Intraocular specimen PCR-positive for infection by herpes simplex virus, varicella zoster virus, or *Toxoplasma gondii* (unless there is immune compromise, morphologic evidence for >1 infection, the characteristic picture of cytomegalovirus retinitis, and the intraocular fluid specimen also has a positive PCR result for cytomegalovirus)

PCR = polymerase chain reaction.

and a second pathogen. In that situation, there should be 2 or more morphologic presentations of retinitis, 1 of which is compatible with CMV retinitis, in order to diagnose CMV retinitis (as well as the positive PCR for CMV). Syphilis can produce a necrotizing retinitis that can be mistaken for CMV retinitis, and it should be excluded.

In CMV retinitis, the retinitis is due to CMV replication in the retina and the attendant retinal destruction, whereas any anterior chamber inflammation and/or vitritis may be due to the immunologic response to CMV,[1] as seen with other infectious retinitides.[35] The increase in vitritis with IRU is consistent with the vitritis being largely part of the immunologic response.[22,23] Immune recovery retinitis has been proposed as an immune recovery inflammatory syndrome (IRIS), with the implication that the immune response contributes to new onset CMV retinitis or worsening of active retinitis within a 3-month window after initiation of ART.[36] However, analysis of a large cohort study of patients with AIDS provided no evidence to support immune recovery retinitis as an IRIS phenomenon,[37] and the amount of lesion opacity in CMV retinitis is inversely related to the degree of immune compromise, the opposite of what would be expected if there was an IRIS-type retinitis.[38] It is more likely that the cases cited to support the concept of immune recovery retinitis merely represented the expected behavior of CMV retinitis in the context of immune compromise observed during the 3-6-month window between the rise in $CD4^+$ T cells after initiating ART and the restoration of immunity to CMV.[5] The available data support the concept that active CMV retinitis is due to CMV replication in the retina.[1]

Classification criteria are used to diagnose individual diseases for research purposes.[33] Classification criteria differ from clinical diagnostic criteria in that, although both seek to minimize misclassification, when a tradeoff is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[33] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process used in this study did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because this study was developing classification criteria and because the typical agreement between 2 uveitis experts on diagnosis was moderate at best,[31] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases which clinicians may diagnose as CMV retinitis may not be classified as such by classification criteria.

In conclusion, the criteria for CMV retinitis outlined in Table 3 appear to perform sufficiently well for use as classification criteria in clinical research.[32]

CREDIT ROLES

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