Predictors for the Prognosis of Retinal Vasculitis in Uveitis Patients and Factors that Characterize Subsets of Retinal Vasculitis

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CERTIFICATE OF APPROVAL

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ABSTRACT

Specific Aims:

This retrospective chart review study of 1,307 uveitis patients was undertaken to examine: (1) the proportion of retinal vasculitis patients in specific subsets of uveitis patients; (2) the characteristics of the identified retinal vasculitis cases and; (3) visual outcome of the identified retinal vasculitis cases and predictors for the outcome.

Methods:

Ophthalmological records of a sample of 1,307 uveitis patients identified from databases at Oregon Health & Science University (OHSU) with at least one visit to the Uveitis clinic at the Casey Eye Institute between August 1985 and December 2008 were reviewed to identify patients with retinal vasculitis. The sample represents approximately 95% of all uveitis patients seen in the Uveitis clinic between August 1985 to present date, and includes 1,237 patients with uveitis with a presumed diagnosis and a subset of 70 patients from 677 patients with uveitis with unclassifiable disease association. Uveitis diagnoses represented by ten or fewer patients were only included when the entity was known to be strongly associated with retinal vasculitis. Demographic and clinical data, including visual outcomes, were collected from the retinal vasculitis patients identified from the sample of 1,307 patients and 34 patients with primary retinal vasculitis. Other covariates were examined to ascertain whether they were predictive of visual acuity outcome improvement of the retinal vasculitis patients.

Results:

Retinal vasculitis was identified in 11.0% of 1,307 studied uveitis patients. Extrapolating the proportion of retinal vasculitis in idiopathic uveitis patients from which only a subset was reviewed, it is presumed that retinal vasculitis may occur in 14.2% of our tertiary referral uveitis patient population. Only 21.2% of these cases had an identifiable systemic-immune mediated disease. Bilateral cases and patients with retinal vasculitis associated with an underlying systemic disease had a better visual outcome than unilateral cases and those affected by primary retinal vasculitis. After adjusting for within-individual correlation and potential confounders, gender, baseline vision, and etiologic sub-groups were associated with improved likelihood of visual acuity improvement.

Conclusion:

Our study is one of the first U.S. studies to examine the association between retinal vasculitis and a variety of uveitis disease subsets in a tertiary referral population, and the first attempt to investigate visual outcome in retinal vasculitis patients. Our findings on frequency of retinal vasculitis identified in association with specific diagnostic subsets of uveitis are novel. Our findings support the observation that retinal vasculitis occurs in diseases not classically classified as systemic vasculitides, and occurs rather rarely in association with classic forms of systemic vasculitides. Patient demographics were mostly consistent with previously published studies on retinal vasculitis. New findings regarding visual outcomes of the identified retinal vasculitis patients are discussed.

INTRODUCTION

Background:

Disease associations

Retinal vasculitis is an inflammatory eye condition involving retinal blood vessels. Retinal vasculitis is an important, but poorly understood vascular disease and is clinically defined as an abnormal appearance of the retinal vasculature due to inflammation (Rosenbaum, Robertson & Watzke, 1991). It is an uncommon disorder that may occur as an isolated idiopathic condition, in association with systemic immune-mediated diseases, or as a complication of infectious disorders. Retinal vasculitis including cases restricted to the eye and those associated with systemic disease occurs in approximately 10% of uveitis patients. The annual incidence of retinal vasculitis is estimated as 1 to 2 per 100,000, but significant regional variation exists (Hughes & Dick, 2003).

Rosenbaum et al. (1991) described sub-categories into which inflammatory conditions involving retinal vessels can be subdivided. The sub-categories are: (1) systemic illnesses such as Behcet's disease and sarcoidosis; (2) retinal vasculitis occurring in a localized area of chorioretinal infection such as in toxoplasmosis, acute retinal necrosis, or retinitis; (3) vaso-occlusive disease, which is often associated with antiphospholipid antibodies such as the lupus anticoagulant; (4) and idiopathic syndromes for patients who do not fit into any of the other subcategories and who have no known systemic manifestations (Rosenbaum et al., 1991).

Many patients develop a systemic or ocular disease before developing retinal vasculitis, but retinal vasculitis may develop as the initial manifestation of another underlying disorder for some patients (Walton & Ashmore, 2003). An extensive number of diseases are associated with retinal vasculitis such as Behcet's disease, multiple sclerosis, sarcoidosis, systemic lupus

erythematosus (SLE) and Vogt-Koyanagi-Harada (VKH) syndrome, as well as ocular diseases such as birdshot retinochoroidopathy. Among the systemic diseases, one that has been described as most commonly associated with retinal vasculitis is Behcet's disease. Retinal vasculitis occurs in 66 to 73% of Behcet's disease cases, and ocular inflammation constitutes one of the major diagnostic criteria for Behcet's disease (Charteris, Champ, Rosenthal & Lightman, 1992). Behcet's disease, sarcoidosis, and multiple sclerosis have been described as the 3 most common systemic diseases associated with ocular vasculititic disorders (Levy-Clarke & Nussenblatt, 2005).

Infectious etiologies of retinal vasculitis include toxoplasmosis, syphilis, Lyme disease, cat scratch disease, herpes simplex, and tuberculosis. Diagnosis of infectious etiology is often a clinical presumption as there are few ophthalmoscopic features to confirm a diagnosis, although culture and modern molecular techniques are often a useful adjunct in diagnosis (Warner, 2004). Infectious retinal vasculitis often accompanies broader ocular involvement such as chorioretinitis and anterior uveitis (Hughes & Dick, 2003). Distinction of an infectious cause that potentially can cause sight loss or even blindness is critical because it relates to the management of immunosuppressive or antimicrobial therapy (Hughes & Dick, 2003).

Graham et al. (1989) described the ophthalmological features of 150 patients with retinal vasculitis and found that 67 (45%) patients had isolated retinal vasculitis, and 83 (55%) had retinal vasculitis associated with systemic inflammatory disease. Of the 150 patients, 39 (26%) had Behcet's disease, 17 had sarcoidosis, 11 had a uveomeningitic illness, 9 had seronegative arthritis and 2 had SLE (Graham, Standford, Sanders, Kasp & Dumonde, 1989). The study found that isolated retinal vasculitis occured more frequently in females (1.5:1); gender distribution is approximately equal in retinal vasculitis associated with systemic disease (Graham et al., 1989).

This study also found that isolated retinal vasculitis tended to involve peripheral vascular sheathing, macular edema, and diffuse capillary leakage, and retinal vasculitis associated with Behcet's disease commonly involved branch vein retinal occlusions in addition to macular edema and diffuse capillary leakage (Graham et al., 1989). In addition, features of periphlebitis with focal vascular leakage were commonly observed in sarcoidosis-associated retinal vasculitis (Graham et al., 1989). The study concluded that different patterns of retinal vasculitis were observed in different systemic inflammatory diseases and a particular association between peripheral vascular sheathing, macular edema and diffuse capillary leakage occurred in isolated retinal vasculitis (Graham et al., 1989).

One study of 1,254 uveitis patients in Serbia observed Behcet's disease, collagen vascular diseases, sarcoidosis and tuberculosis were commonly associated with retinal vasculitis (Paovic J., Paovic P. & Vukosavljevic, 2009). In this study, retinal vasculitis was most commonly associated with sarcoidosis as it occurred in 37.5% of sarcoidosis patients, and primary retinal vasculitis occured in 6.8 % of total uveitis patients (Paovic et al., 2009). Cotton wool spots were involved in 38.3%, retinal hemorrhages in 34% and venous sheathing in 25.1% of all retinal vasculitis cases (Paovic et al., 2009).

Clinical manifestations

Retinal vasculitis is detected clinically upon ophthalmologic examinations or demonstrable by fluorescein angiography of the fundus. The most characteristic feature of retinal vasculitis is retinal vascular sheathing. Focal areas of cuffing as well as "skip areas" are also commonly seen with no apparent sheathing (Walton & Ashmore, 2003). Vascular sheathing is one of the most indicative signs of retinal vasculitis but is not specific as it may appear, as it also

may appear in non-inflammatory conditions, for example following a retinal vein occlusion (Rosenbaum et al., 1991). Retinal vasculitis also can result in other findings such as cotton-wool spots or cytoid bodies and retinal hemorrhage (Rosenbaum et al., 1991). While retinal veins are most commonly affected, retinal arteries and capillaries may also be involved (Walton & Ashmore, 2003). Anterior chamber cells, vitritis, inferior vitreous snowballs, and posterior vitreous detachment are also common (Walton & Ashmore, 2003). Chronic complications often associated with a poor visual prognosis include branch vein occlusion, central vessel occlusion, macular ischemia, persistent neovascularization, vitreous hemorrhage, and tractional retinal detachment (Walton & Ashmore, 2003). Many of these clinical signs can be confirmed by fluorescein angiography.

Retinal vasculitis may be either symptomatic or asymptomatic. The most common symptoms reported by patients include blurred or decreased vision, floaters and scotomata. Decreased vision and floaters are often associated with inflammation of the posterior retinal blood vessels and /or vitreous cells, and scotomata are usually related to the areas of ischemia (Abu El-Asrar, Herbort & Tabbara, 2005). However, if the vasculitis is confined to the periphery of the fundus without vitreous involvement, it may have minimal symptoms or no symptoms (Abu El-Asrar et al., 2005). In addition, systemic symptoms and signs including oral and genital ulcers, skin ulceration, arthritis, rash, neurologic, pulmonary, renal, or gastrointestinal and evidence of embolic disease may suggest an underlying etiology.

Diagnostic evaluation

A diagnostic evaluation to search for an underlying cause is often multidisciplinary and involves clinical examinations, a detailed review of medical history, and laboratory investigations (Herbort, Cimino & Abu El-Asrar, 2005). Instruments such as a direct ophthalmoscope, an indirect ophthalmoscope, or the combination of a slit-lamp biomicroscope with an appropriate contact lens can be used to directly visualize retinal vessels (Rosenbaum et al., 1991). When it is difficult to directly visualize small patches of vasculitis or peripheral retinal involvement, fluorescein angiography can be used for further evaluation. Fluorescein angiography is an essential component of retinal vasculitis evaluation and management. Fluorescein angiography demonstrates leakage of dye due to breakdown of the inner blood-retinal barrier, and staining of the blood vessel wall with fluorescein (Abu El-Asrar et al., 2005). Features demonstrated by fluorescein angiography include inflammatory and ischemic manifestations such as vascular staining and leakage, retinal neovascularization and sclerosis of vessels (Walton & Ashmore, 2003). Fluorescein angiography is often more sensitive than clinical examinations and frequently reveals more extensive vasculitis than suggested upon clinical examinations. In addition to clinical examinations, commonly performed diagnostic evaluations include complete blood count, erythrocyte sedimentation rate, chemistry panel, venereal disease research laboratory test, urinalysis, tuberculin skin testing, human immunodeficiency virus serology, chest radiograph and neuroimaging (Abu El-Asrar, Herbort & Tabbara, 2010). Discrimination between different etiologies of retinal vasculitis is critical because their treatment is different; immunosuppressive therapy may be essential for retinal vasculitis associated with systemic disease but deleterious in retinal vasculitis of infectious etiology (Abu El-Asrar et al., 2005).

Treatment options

The goal of treatment of retinal vasculitis is to suppress the intraocular inflammation to prevent visual loss and complications. Because there is no cure for retinal vasculitis, the overall management aims to maintain the optimal visual acuity and control the disease activity (Standford & Verity, 2000). Patients with mild disease activity and good visual acuity (at least 20/40) may not need intervention or therapy to control their disease (Walton & Ashmore, 2003). However, for patients with greater than moderate inflammation, the most common initial therapy consists of corticosteroid therapy. Oral steroid therapy is used for patients with moderate to severe bilateral disease and a significant drop of visual acuity (Walton & Ashmore, 2003). Some patients may respond rapidly, but others may require high-dosage and will not show clinical improvement until 3 to 4 weeks following initiation. Steroid therapy remains the first line of treatment for retinal vasculitis due to rapid action and extensive experience with a long historical use. Periocular corticosteroids are often used in patients with unilateral disease or moderately severe inflammation (Walton & Ashmore, 2003). Periocular steroids have relatively few side effects apart from raised intraocular pressure. Other complications include cataract, local discomfort, ptosis, orbital fat herniation, worsening of infection and rarely, permanent visual loss. Studies have shown that up to 80% of patients will improve, and that patients whose visual acuity has not fallen significantly often respond better (Standford & Verity, 2000). Besides periocular steroid injections, intravitreal injections are also used, particularly in refractory cases (Standford & Verity, 2000). Intravitreal injections may clear macular edema with some visual improvement, but increase the risk of steroid-induced glaucoma and cataract formation (Standford & Verity, 2000).

Despite the high success rate with steroid therapy, some patients may show no or inadequate response to these drugs and many patients may experience side effects. Steroid-sparing immunosuppressive therapy then may be used for the management of the disease. Mycophenolate mofetil, cyclosporine and azathioprine are widely-used immunosuppressive agents for retinal vasculitis treatment. Other therapies include methotrexate and biologic immunosuppressive agents such as infliximab, which is a monoclonal antibody directed against tumor necrosis factor alpha (TNF-α) (Standford & Verity, 2000). Although biologic agents may be effective in rapidly controlling the disease, their toxicity is of concern and side effects are also common.

In order to treat complications associated with retinal vasculitis such as widespread ischemic retinal vasculitis and recurrent vitreous hemorrhages, laser and surgical treatment may be necessary (Standford & Verity, 2000). Laser photocoagulation and vitreoretinal surgical procedures are common examples. Laser photocoagulation is used to treat persistent neovascularization as well as patients with neovascular glaucoma and vitrectomy is used for persistent vitreous hemorrhage, tractional retinal detachment, and epiretinal membrane removal (Abu El-Asrar et al., 2005).

Presence of an associated condition, severity of the disease, and the laterality (unilateral vs. bilateral) are important factors in determining appropriate treatment for retinal vasculitis (Rosenbaum et al., 1991). For example, if the disease has an infectious etiology, an antibiotic therapy would be appropriate. If the cause is not infectious, periocular corticosteroid administration may be appropriate to help control the inflammation (Rosenbaum et al., 1991).

Complications and disease outcome

It is difficult to predict visual outcome in patients with retinal vasculitis as the course of the disease may vary (Standford & Verity, 2000). Retinal vasculitis patients may develop complications such as cytoid macular edema, macular ischemia and epiretinal membrane. The macula is the center of the retina with a dense population of cone photoreceptors responsible for fine visual discrimination and color vision. Macular edema is a complication of venous occlusion or blood retinal barrier breakdown and leakage and is one major cause of vision loss (Hughes & Dick, 2003). Cytoid macular edema is a significant factor contributing to poor vision in retinal vasculitis although a good prognosis can be expected with adequate treatment with immunosuppressive therapy (Abu El-Asrar, Herbort & Tabbara, 2009). Macular ischemia also has devastating visual consequences. Macular ischemia may result not only from retinal vasculitis but also from the underlying choroid (Hughes & Dick, 2003). Poor visual outcome is observed in some cases of retinal vasculitis despite adequate therapy, and can often be explained by other complications such as macular ischemia on fluorescein angiography. Some cases of severe retinal vasculitis are neither associated with a systemic disease nor characterized in the ophthalmic literature (Levy-Clarke & Nussenblatt, 2005). Systemic disease may become manifest in patients with prolonged primary retinal vasculitis (Standford & Verity, 2000).

Rationale:

Retinal vasculitis is relatively rare and yet is potentially vision threatening. Retinal vasculitis can progress rapidly leading to complications and ultimately irreversible vision loss. An early diagnosis, referral, and selection of optimal treatment are critical for proper management of the disease. There are only a limited number of publications related to this disease and well-controlled clinical trials have not been conducted in patients with retinal vasculitis (Standford & Verity, 2000). Current treatment guidelines are based on limited studies, and the evaluation and treatment of retinal vasculitis patients are thus often challenging (Standford & Verity, 2000). Most of currently available studies are not United States population-based, and as geography greatly affects incidence of the disease, it is critical to have a U.S.-based study. In this study, data from retrospective chart reviews of uveitis patients seen at the Uveitis clinic at Casey Eye Institute were analyzed to investigate the occurrence of retinal vasculitis in specific subsets of uveitis patients, and to examine the visual outcome of identified retinal vasculitis cases and predictors of prognosis. The main goal of this study was to provide information that would be useful in developing guidelines for early diagnosis and treatment for retinal vasculitis, and in creating interventions aimed at improving disease outcome.

METHODS

Study population and data collection:

From databases at Oregon Health & Science University (OHSU), we identified uveitis patients with at least one visit to the Uveitis clinic at the Casey Eye Institute between August 1985 and December 2008. Our databases were updated up to 2008, and therefore represent approximately 95 % of the uveitis patient population seen up to that date. Thirty four uveitis patients with primary retinal vasculitis without an associated disease, 1,366 patients with uveitis with a presumed diagnosis, and 677 patients with uveitis with unclassifiable disease association were identified.[1] The diagnosis of associated diseases included acquired immune deficiency syndrome (AIDS), cytomegalovirus (CMV), ankylosing spondylitis (AS), acute retinal necrosis (ARN), Behcet's syndrome, birdshot retinochoroidopathy, Crohn's disease, herpes simplex virus (HSV), herpes zoster virus (HZV), juvenile idiopathic arthritis (JIA), lymphoma, melanoma, multiple sclerosis (MS), pars planitis, psoriatic arthritis, sarcoidosis, scleritis, syphilis, sympathetic ophthalmia, tuberculosis, tubulointerstitial nephritis and uveitis (TINU), toxoplasmosis, ulcerative colitis (UC) and Vogt-Koyanagi-Harada (VKH). Charts for diagnoses represented by ten or fewer patients were only reviewed when the entity was known to be strongly associated with retinal vasculitis such as AIDS and tuberculosis. Of these 1,366 patients, both electronic and paper based ophthalmological records of 1,307 patients were available to identify those with evidence of retinal vasculitis. Fifty nine patients whose charts could not be located were excluded. Evidence of retinal vasculitis was defined as vascular sheathing, intraretinal hemorrhage, cotton wool spot or vascular occlusion noted in records of ophthalmological examinations or findings consistent with retinal vasculitis by flourescein angiography at any point in time while being seen at the Uveitis clinic. From the alphabetized list

of the 677 patients with unclassified disease association, every 8th patient was extracted for sampling. Among the 84 selected patients, all available ophthalmological records of 70 patients were reviewed to identify those with retinal vasculitis, excluding 14 patients whose records could not be located.

Study data were collected retrospectively from the ophthalmologic records of patients identified as having retinal vasculitis with an underlying disease and patients with primary retinal vasculitis without disease association. All patients had at least one visit to the Uveitis clinic but no minimum follow-up time was required; follow-up periods were therefore not contiguous for all patients. Information retrieved from the charts of the identified patients included the following: uveitis diagnosis; disease onset (i.e. sudden or insidious) as defined as the timing of initial clinical symptoms as noted by the caring ophthalmologist; follow-up time as defined as the time between baseline evaluation (first visit to the Uveitis clinic upon referral) and last visit; time between disease onset and baseline evaluation; best corrected visual acuity with pinhole improvement at baseline evaluations and at final visit; laterality of uveitis (unilateral or bilateral); age at disease onset; age at baseline evaluation; and demographic information including gender and ethnicity.

Main outcome variable:

Best corrected Snellen visual acuity with pinhole improvement at baseline evaluation and at final visit were recorded for every eye for the uveitis patients identified as having evidence of retinal vasculitis or diagnosed with primary retinal vasculitis. Vision of counting fingers and hand motion were recorded as 20/2,000 and 20/20,000 respectively (Holladay, 1997). Four patients with light perception with projection and no light perception vision were excluded. As

the lines on the Snellen visual acuity chart follow a geometric progression, the LogMAR (log of the minimum angle of resolution) notation was used to compute visual acuity change and average (Holladay, 1997). The LogMAR was computed by taking the negative of the logarithm of the decimal notation of the Snellen aquity, eg, 20/100 = 0.20 and the negative of the log of 0.2 is + 0.7. The average of 20/20 and 20/100 vision is 0.35 LogMAR units. Antilog of the negative of the LogMAR was taken to convert back to decimal acuity, eg, antilog of the negative of 0.35 is 0.45, which corresponds to 20/45 Snellen acuity.

Statistical analysis:

Statistical methods included descriptive statistics, chi-square test, Kaplan-Meier estimator, Cox proportional-hazards regression and Cox proportional-hazards model with shared frailty. Mean and frequency tables for predictor and outcome variables were performed for descriptive analysis. Among the 178 patients identified as having retinal vasculitis, analysis of visual acuity was performed for 98 patients for whom visual acuity was available at least at two different time points. Because the incidence of vision change varied over time, a time-to-event approach was used to evaluate visual acuity change over time. Time-to-event outcomes and the proportions of vision improvement at least by 2 lines of Snellen acuity were computed using the Kaplan-Meier method and Cox regression. The event of interest was defined as improvement in vision by at least by 2 lines, and therefore the Kaplan-Meier curves depict the probability of not improving vision by at least 2 lines as a function of follow-time for the first part of the Kaplan-Meier analysis. The 98 patients (172 eyes) were followed up in the survival proportions until they improved their vision at least by 2 lines, or until their last visit (lost-to-follow up). Kaplan-Meier curves were generated for all cases, by laterality, by disease association, and by etiologic

subcategories. Cox proportional hazards model was employed to examine the relationship between vision improvement and other covariates, while controlling for the effects of potentially confounding variables such as demographic characteristics. Multivariate analysis was performed using Cox proportional hazard ratio model. Time-to-event outcomes and the proportions of vision worsening by at least 2 lines of Snellen acuity over time were also computed similarly using the Kaplan-Meier method. Kaplan-Meier curves were generated to depict the probability of vision worsening at least by 2 lines; the 98 patients were followed up in the survival proportions until they experienced vision worsening at least by 2 lines, or until they were lost to follow up. Kaplan-Meier curves for vision worsening were generated for all cases, by laterality, by disease association, and by etiologic sub-categories. Because each affected eye was treated as an independent individual, Cox model with shared frailty was employed to account for the within-individual correlation. All statistical analysis was performed using Stata version 11.0 (Stata, College Station, Texas).

Human subjects protections:

The study was reviewed and approved by the Institutional Review Board (IRB) at OHSU. The study has received a waiver of the HIPAA Authorization requirement and therefore formal informed consent was not sought from patients whose charts were reviewed. Data files were placed on secured OHSU network drives requiring an OHSU network ID and a password. The data generated contained patient identifiers, but every effort has been made to minimize the use of such identifiers to prevent the loss of confidentiality. Analysis of this dataset did not contain any information regarding patients' identity.

RESULTS

Characteristics of 178 retinal vasculitis patients:

One hundred forty-four patients with retinal vasculitis with an associated uveitis diagnosis and 34 primary retinal vasculitis patients were identified, of whom 86 (48.3%) were male, 127 (71.4%) White, 10 (5.6%) Black, 8 (4.5%) Asian, 13 (7.3%) Hispanic, 9 (5.1%) multi-racial, and 11 (6.2%) were of unknown race (Table 1). Bilateral cases were more common than unilateral cases; 120 patients (72.3%) had bilateral conditions and 46 (27.3%) unilateral. Laterality could not be determined for 12 patients due to incomplete or missing records. Median age at onset was 36.0 in years and average was 37.0 (S.D. 20.0; range 0.67 to 78) for 159 patients of whom 15 (9.4%) were 10 years old and under, 21 (13.2%) between 11 and 20 years, 61 (38.4%) between 21 and 40 years, 37 (23.3 %) between 41 and 60 years, and 25 (15.7%) 61 years and older. The age at disease onset was unknown for 19 patients. The median age at first visit to the Uveitis clinic upon referral was 38 and average was 39.7 in years (S.D. 19.6; range 1 - 79).

Table 1 *Characteristics of 178 uveitis patients with retinal vasculitis*

Characteristics		*Number*	*Percentage*
Gender	Male	86	48.3%
	Female	92	51.7%
Race	White	127	71.4%
	Black	10	5.6%
	Asian	8	4.5%
	Hispanic	13	7.3%
	Multi-racial	9	5.1%
	Unknown	11	6.2%
Laterality	Unilateral	46	25.8%
	Bilateral	120	67.4%
	Unknown	12	6.7%
Age at onset (years)	[Median: 36]	[Average: 37.0(S.D. 20.0)]	[Range: 0.7-78]
	10 years & under	15	8.4%
	11 – 20 years	21	11.8%
	21 – 40 years	61	34.3%
	41 – 60 years	37	20.8%
	61 and older	25	14.0 %
	unknown	19	10.7%
Age at baseline evaluation (years)	[Median: 38]	[Average: 39.7(S.D. 19.6)]	[Range: 1-79]

Retinal vasculitis cases in uveitis with an underlying disease:

One thousand three-hundred seven charts of patients with uveitis associated with an underlying classifiable form of uveitis were reviewed to identify 144 (11.0%) patients with retinal vasculitis. Table 2 summarizes the number of patients identified categorized by uveitis diagnosis. The proportion of retinal vasculitis cases was highest for uveitis associated acquired immune deficiency syndrome (AIDS) and/or cytomegalovirus (CMV) and tuberculosis; 3 (42.9%) out of 7 AIDS/CMV patients and 1 (33.3%) of 3 tuberculosis patients had retinal vasculitis. However, the number of patients screened for each of these diagnoses constituted less than 1% of all uveitis patients reviewed. Among the uveitis diagnoses for which the number of

patients reviewed constituted at least 1% of total uveitis cases, retinal vasculitis occurred most commonly in association with Behcet's disease (28.6%) followed by birdshot choroidopathy (26.5%), acute retinal necrosis (ARN) (22.7%), and idiopathic uveitis with unclassifiable disease association (21.4%). Retinal vasculitis was found only in 1 (0.8%) of 133 patients with ankylosing spondylitis (AS) associated uveitis. No charts were located for the 4 patients with uveitis associated with melanoma.

Table 2 *Number of retinal vasculitis patients identified in 1,307 uveitis patients (by uveitis diagnosis)*

Uveits Diagnosis	*No. of patients screened*	*No. of patients with retinal vasculitis*	*% of patients with retinal vasculitis*
AIDS/CMV	7	3	42.9%
Ankylosing Spondylitis	133	1	0.8%
Acute Retinal Necrosis	22	5	22.7%
Behcet's Disease	42	12	28.6%
Birdshot Choroidopathy	34	9	26.5%
Crohn's Disease	10	1	10.0%
Herpes Simplex	45	2	4.4%
Herpes Zoster	33	2	6.1%
Juvenile Inflammatory Arthritis	94	4	4.3%
Lymphoma	16	2	12.5%
Multiple Sclerosis	24	4	16.5%
Pars Planitis	194	36	18.6%
Psoriatic Arthritis	24	3	12.5%
Sarcoidosis	148	13	8.8%
Scleritis	242	12	5.0%
Syphilis	7	2	28.6%
Sympathetic Ophthalmia	11	1	9.1%
Tuberculosis	3	1	33.3%
Interstitial Nephritis	32	1	3.1%
Toxoplasmosis	48	7	14.6%
Ulcerative Colitis	11	1	9.1%
Vogt-Koyanagi Harada	57	7	12.3%
Idiopathic (unclassified)	70	15	21.4%
Total	1,307	144	11.0%

The 144 retinal vasculitis patients with uveitis with a presumed diagnosis were divided into ocular syndrome, systemic/ immune-mediated, infectious, masquerade and idiopathic etiologic subcategories. The ocular syndrome etiologic subcategory included primary retinal vasculitis, birdshot retinochoroidopathy, sympathetic ophthalmia and pars planitis. The immune-mediated/systemic group included AS, Behcet's disease, Crohn's disease, juvenile idiopathic arthritis (JIA), multiple sclerosis (MS), Vogt-Koyanagi-Harada syndrome (VKH), ulcerative colitis (UC), psoriatic arthritis, scleritis and sarcoidosis. The infectious category included syphilis, tuberculosis, toxoplasmosis, herpes simplex virus (HS), herpes zoster virus (HZV), ARN and AIDS and/or CMV. The idiopathic etiology consisted of retinal vasculitis cases in uveitis with no known systemic disease association and no pattern of uveitis to fit into a specific diagnostic category such as birdshot retinochoroidopathy. Table 3 summarizes the number of uveitis cases reviewed and retinal vasculitis cases identified by etiologic sub-categories. Retinal vasculitis was most commonly found in patients with idiopathic uveitis, identified in 15 (21.4%) out of 70 (Table 2). Retinal vasculitis was also commonly found in uveitis associated with ocular syndrome, found in 46 (19.2%) out of 239 patients, not including those with primary retinal vasculitis. 22 (13.3%) out of 165 patients in the infectious sub-group, 2 out of 16 (12.5%) in the masquerade sub-group, and 59 (7.2%) out of 817 in systemic- immune-mediated sub-group were identified as having retinal vasculitis. A majority of all uveitis patients reviewed in the systemic/ immune-mediated etiologic sub-group consisted of scleritis, sarcoidosis and AS patients as they constituted 29.6%, 18.1% and 16.3% of all cases in this sub-group respectively.

Table 3 *Number of patients with retinal vasculitis identified among 1,307 uveitis patients (by etiologic subcategory)*

Etiologic subcategory	*No. of patients*	*No. of patients with retinal vasculitis*	*% of patients with retinal vasculitis*
Ocular syndrome	239	46	19.2%
Systemic, Immune-mediated	817	59	7.2%
Infectious	165	22	13.3%
Masquerade	16	2	12.5%
Idiopathic	70	15	21.4%
Total	1,307	144	11.0%

The 178 retinal vasculitis patients in the dataset were followed up in clinic for varying lengths of time, as some were seen only once and some returned for follow-up for as long as 207 months. Figure 1 plots change in LogMAR from baseline evaluation to final visit corresponding to varying follow-up time in months. Positive change in LogMAR corresponds to vision improvement from baseline. Patients with shorter follow-up time tended to have a greater change in LogMAR compared to those with longer follow-up time. The average baseline LogMAR was 0.42 for the 97 eyes that were evaluated only once (S.D. 0.57; range -0.12 - 3), LogMAR 0.37(S.D. 0.56; range -0.12 - 3) the 172 eyes with follow-up time of greater than 0 months, and was 0.39 (S.D. 0.56; range 0.12 - 3) for all 259 affected eyes (Table 4). Corresponding Snellen acuity was approximately 20/50 for the 97 eyes and 20/45 for the 172 eyes respectively; those that were evaluated more than once had better baseline vision than the 97 eyes evaluated only once. Baseline visual acuity was not available for 17 patients due to incomplete records and 4 patients with light perception with projection and no light perception vision were excluded.

Figure 1 Change *in LogMAR from baseline evaluation to final visit corresponding to varying lengths of follow-up time in months (Positive change in LogMAR corresponds to improvement)*

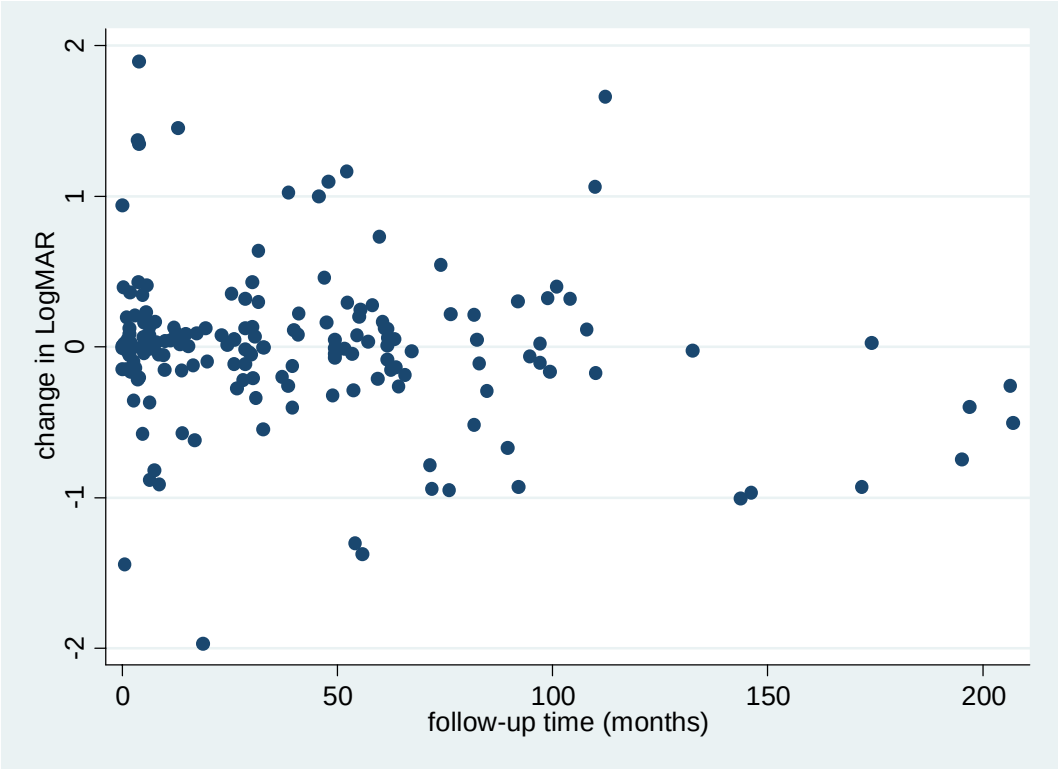


Table 4 *Baseline LogMAR of 157 patients (269 affected eyes; 224 eyes in bilateral cases, 45 eyes in unilateral cases)*

	Median	*Average*	*Range*
LogMAR at baseline evaluation			
Eyes with follow-up = 0 months (97 eyes)	0.18	0.42 (S.D. 0.57)	-0.12 – 3
Eyes with follow-up > 0 months (172 eyes)	0.18	0.37 (S.D. 0.56)	-0.12 – 3
All affected eyes (269 eyes)	0.18	0.39 (S.D. 0.56)	-0.12 – 3

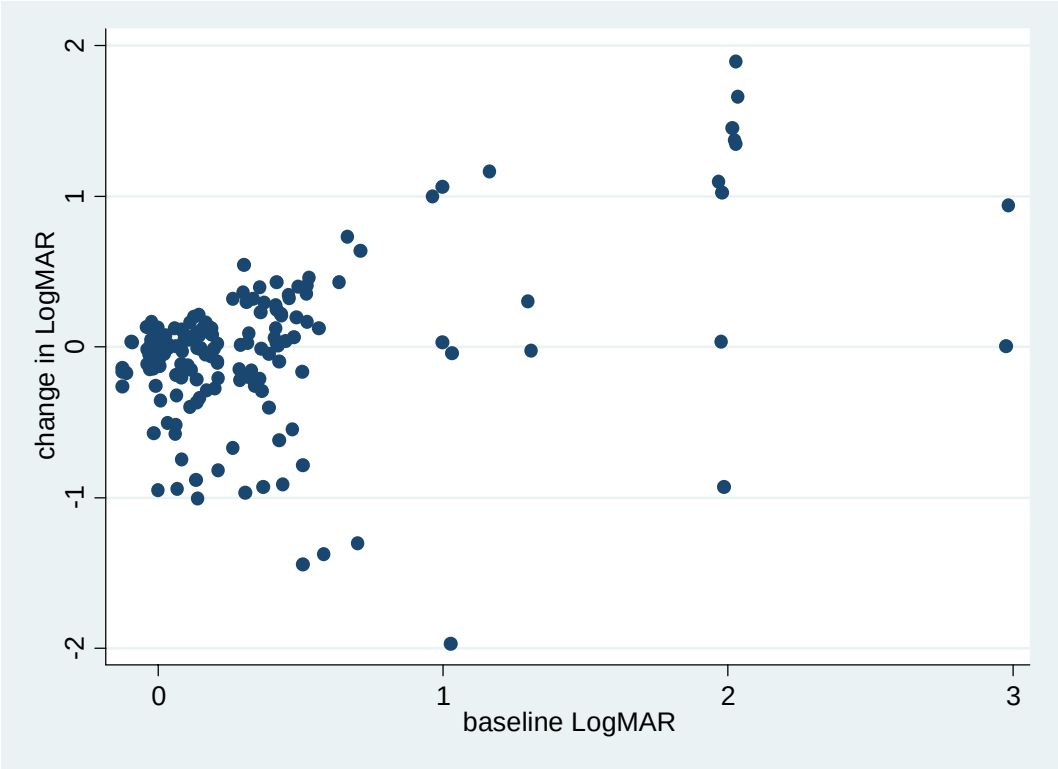
Visual acuity change in 98 retinal vasculitis patients with follow-up time greater than 0 months:

Eighty out of 178 retinal vasculitis patients in the study dataset only had 1 visit to the Uveitis clinic. Table 5 summarizes follow-up time and time from onset to first visit for the remaining 98 patients with follow-up time greater than 0 months. Median follow-up time was 31 months and average was 41.9 (S.D. 44.3; range 0.5 - 207). Time from disease onset to baseline evaluation was 34.2 months on average (S.D. 49.7; range 0 - 192) and could not be determined for 8 eyes whose onset was unknown.

Table 5 *Follow-up time and time from onset to first visit for 98 patients (172 affected eyes) with follow up time greater than 0 months (24 Unilateral cases; 74 Bilateral cases)*

Follow-up time (Months)	Median: 31	Average: 41.9 (S.D. 44.3)	Range: 0.5–207
Time from onset to baseline evaluation (Months)	Median: 8	Average: 34.2 (S.D. 49.7)	Range: 0-192
	Under	N = 12	7.0%
	1 – 5 months	55	32.0%
	6 – 10 months	16	9.3%
	11 – 20 months	21	12.2%
	21 – 50 months	25	14.5%
	51 – 100 months	12	7.0%
	101 months and longer	23	13.4%
	Unknown	8	4.7%

Figure 2 *LogMAR change from baseline evaluation to final vs. logMAR at baseline evaluation in 98 patients with follow-up time greater than 0 months (Positive change in LogMAR corresponds to vision improvement)*



In order to examine whether baseline visual acuity affects prognosis (eg, outcome in a patient with 20/20 vision at baseline vs. in a patient with 20/100 vision at baseline), LogMAR change from baseline evaluation to final visit is plotted as a function of baseline LogMAR (Figure 2). Change in LogMAR tends to be greater for those with higher LogMAR, corresponding to worse Snellen vision; patients with Snellen visual acuity close to 20/20 at baseline tend to remain stable.

Table 6 summarizes number of line change in Snellen visual acuity from baseline to final visit per eye-year of the 98 patients (172 affected eyes), of which 24 were unilateral cases and 74 bilateral. The average number of line change per eye-year for all affected eyes (172 eyes) was 2.0 lines (S.D. 18.1; range -58.2 -130). Among the 172 eyes, the 148 eyes involved in bilateral

uveitis improved by 2.6 lines on average per eye-year (S.D. 18.2; range -30.0 - 120), and the 24 eyes in unilateral uveitis worsened by 0.03 lines per eye-year on average (S.D. 17.6; range -58.2 - 53.2). Visual acuity of the 22 eyes affected by primary retinal vasculitis without disease association improved on average by 2.3 lines in Snellen visual acuity per eye-year (S.D.19.2; range -58.2 - 120) from baseline to final visit, and 150 eyes retinal vasculitis with an underlying disease improved by 0.1 (S.D. 6.3; range, 19.8 - 21.1) lines per eye-year (Table 7). Median was 0 lines of change for both groups. Among the 172 affected eyes, 36 eyes improved by equal to or greater than 2 lines on Snellen acuity, 41 worsened by equal to or greater than 2 lines (Table 6). 53 eyes changed by less than 2 lines and 42 did not change vision.

Table 6 *Snellen visual acuity line change per eye-year in 98 retinal vasculitis patients (172 affected eyes) with follow-up time > 0 months (24 Unilateral cases; 74 Bilateral cases)*

	Median	*Average*	*Range*
Rate of visual acuity change			
All affected eyes (172 eyes)	0	2.0 (S.D. 18.1)	-58.2 – 130
Bilateral (148 eyes)	0	2.6 (S.D. 18.2)	-30.0 – 120
Unilateral (24 eyes)	-0.09	-1.7 (S.D. 17.6)	-58.2 – 53.2

Table 7 *Snellen visual acuity line change per eye-year in 98 retinal vasculitis patients (172 affected eyes) with and without underlying disease*

	Median	*Average*	*Range*
Primary retinal vasculitis without disease association (22 eyes)	0	2.3 (S.D. 19.2)	-58.2 – 120
Retinal vasculitis with disease association (150 eyes)	0	0.1 (S.D. 6.3)	-19.8 – 21.1

Table 8 *Number of eyes by visual acuity change*

	By < 2ines	*by ≥ 2ines*
Improvement	*29*	*36*
worsening	*24*	*41*
No change	*42*	

Figures 3 through 6 depict the proportions of eyes which have not achieved vision improvement by at least 2 lines as a function of follow-up time. The tick marks represent censored cases. Among the 172 eyes examined, vision improvement was achieved for 1 eye (0.58%) as early as at 0.5 months of follow-up (Figure 3). At 10 months of follow-up, improvement was achieved for 12 eyes (7.0%); 45 eyes (26.2%) were lost-to-follow up at this time. At 50 months of follow-up, 21 (13.2%) eyes achieved vision improvement; 89 eyes (55.5%) were lost-to-follow up at this time. Bilateral cases achieved vision improvement in a greater proportion than unilateral cases (Figure 4), and cases with a presumed uveitis diagnosis were more likely to improve vision than primary retinal vasculitis cases (Figure 5).

Figure 3 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not achieved vision improvement by at least 2 lines as a function of follow-up time in months*

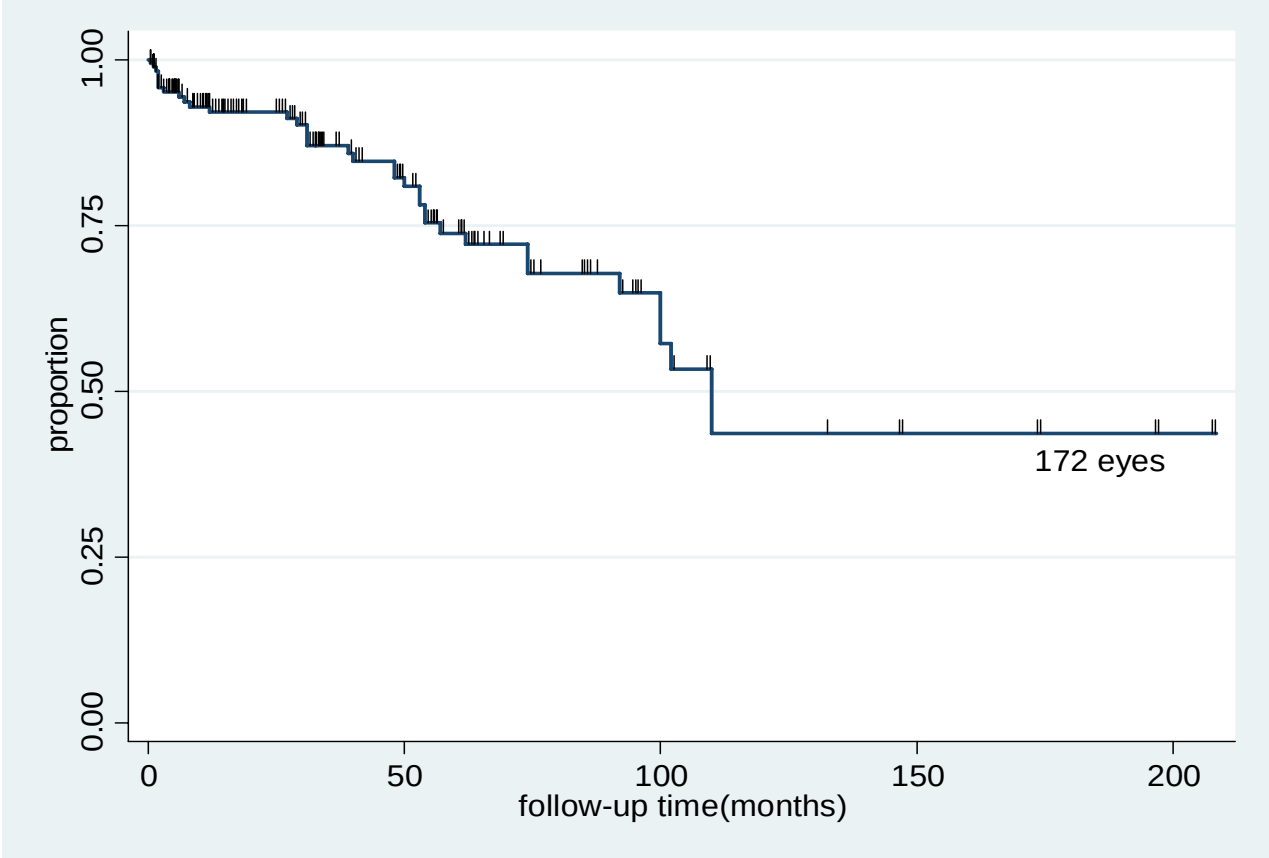


Figure 4 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not achieved vision improvement of at least 2 lines as a function of follow-up time in months (by laterality)*

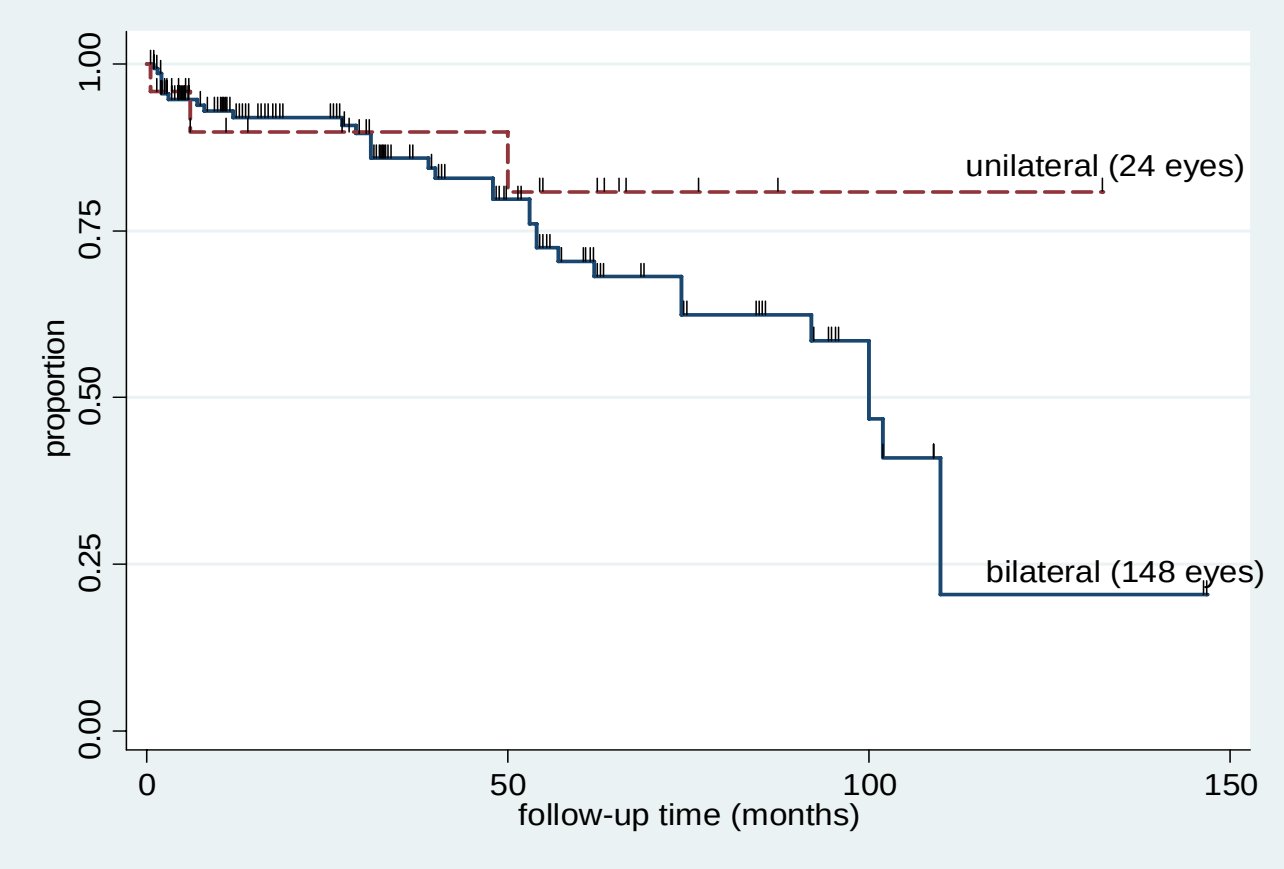


Figure 5 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not achieved vision improvement of at least 2 lines as a function of follow-up time in months (by association)*

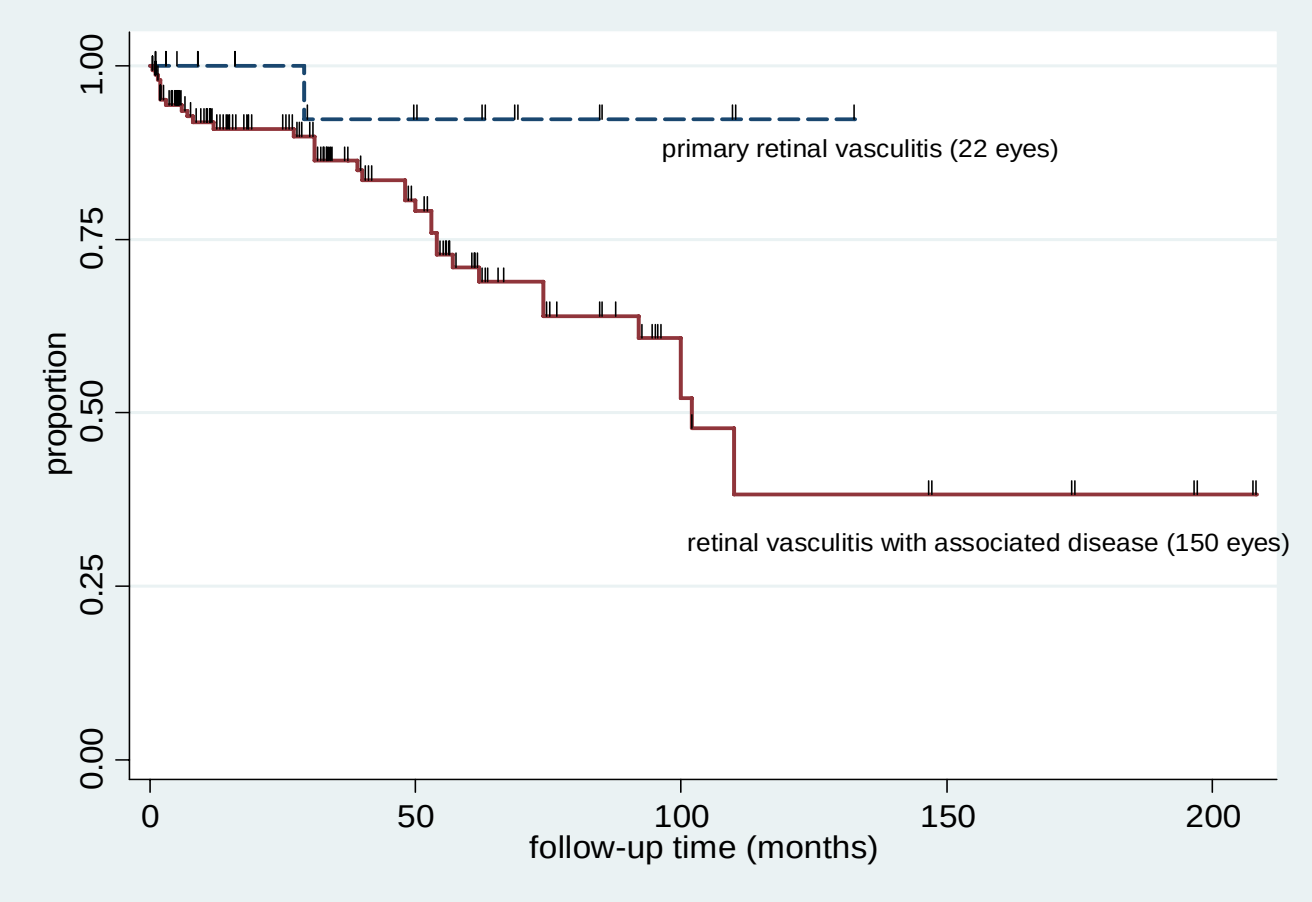
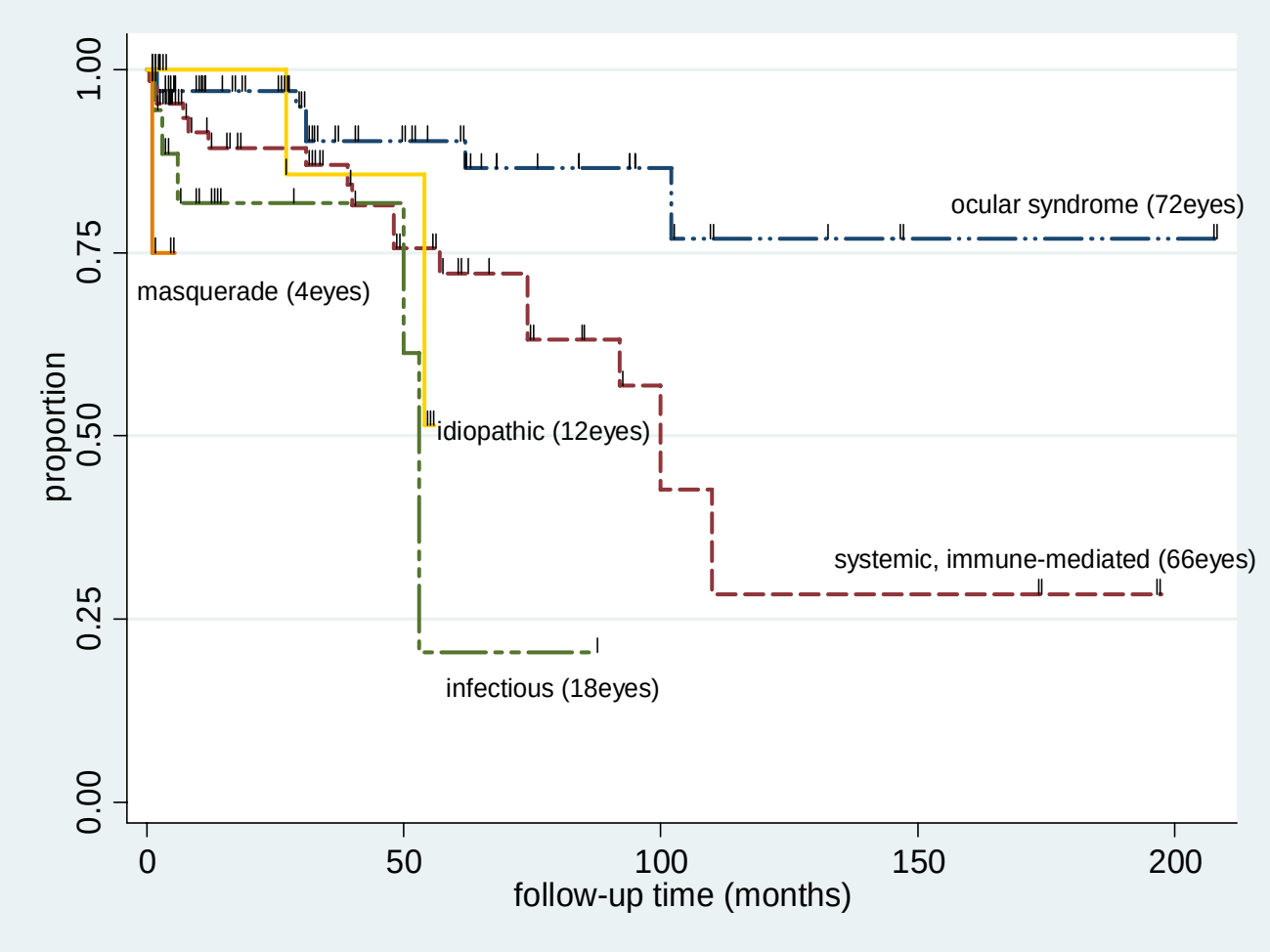


Figure 6 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not achieved vision improvement of at least 2 lines as a function of follow-up time in months (by etiologic sub-category)*



Figures 7 through 10 depict the proportions of affected eyes, which have not experienced vision worsening by at least 2 lines on Snellen acuity as a function of follow-up time. The tick marks represent censored cases. Among the 172 eyes examined, 1 eye had vision worsening vision by at least 2 lines at 1 month of follow-up (0.58%) (Figure 7). At 10 months of follow-up, 9 eyes had vision worsening by at least 2 lines (5.2%); 47 eyes (27.3%) were lost-to-follow up at this time. At 50 months of follow-up, 31 (18.0%) eyes experienced vision worsening by at least 2

lines; 92 eyes (53.5%) were lost-to-follow up at this time. Unilateral cases were more likely to experience vision worsening than bilateral cases (Figure 8), and a greater proportion of cases with uveitis with a presumed diagnosis experienced vision worsening than those with primary retinal vasculitis (Figure 9).

Figure 7 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not experienced vision worsening by at least 2 lines as a function of follow-up time in months*

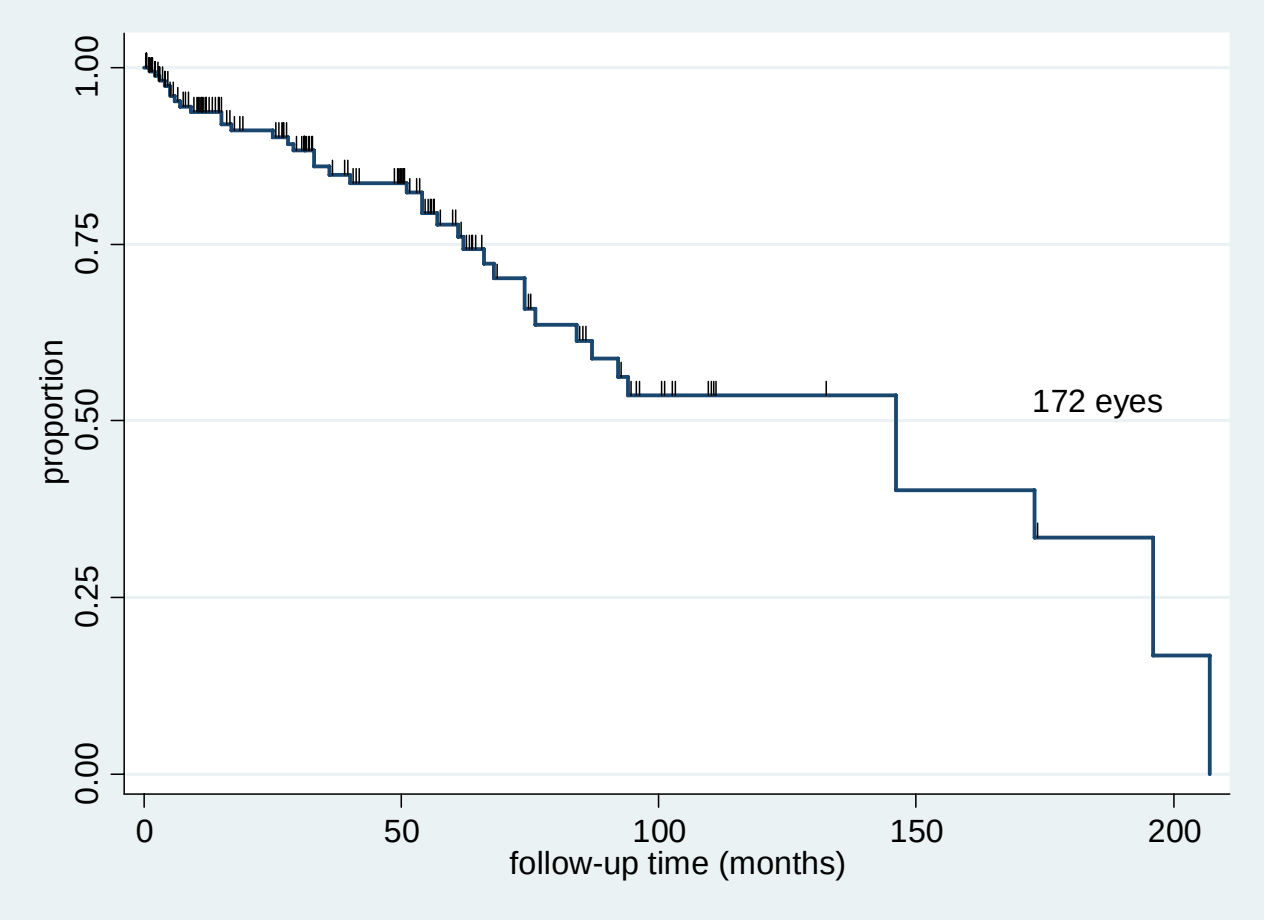


Figure 8 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not experienced vision worsening by at least 2 lines as a function of follow-up time in months (by laterality)*

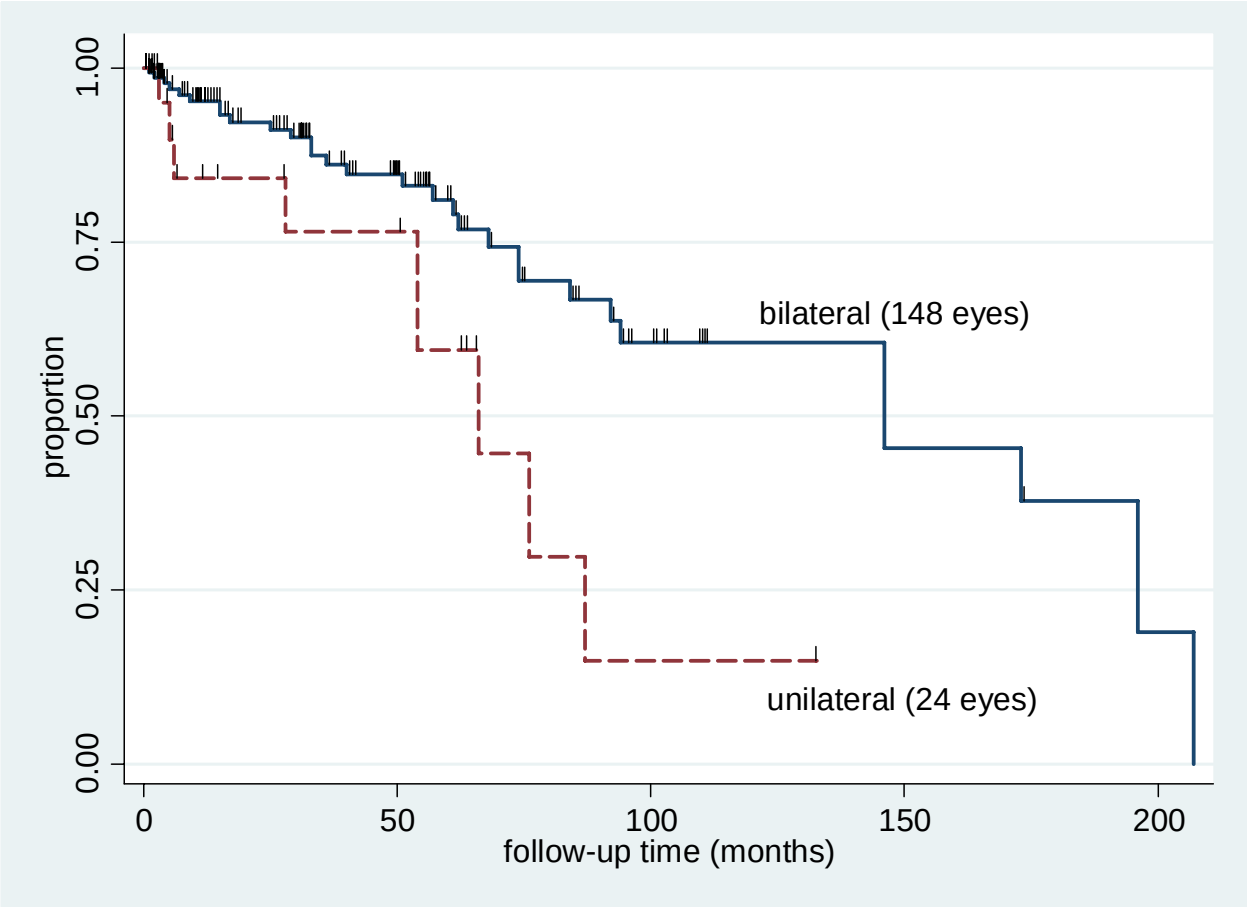


Figure 9 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not experienced vision worsening by at least 2 lines as a function of follow-up time in months (by association)*

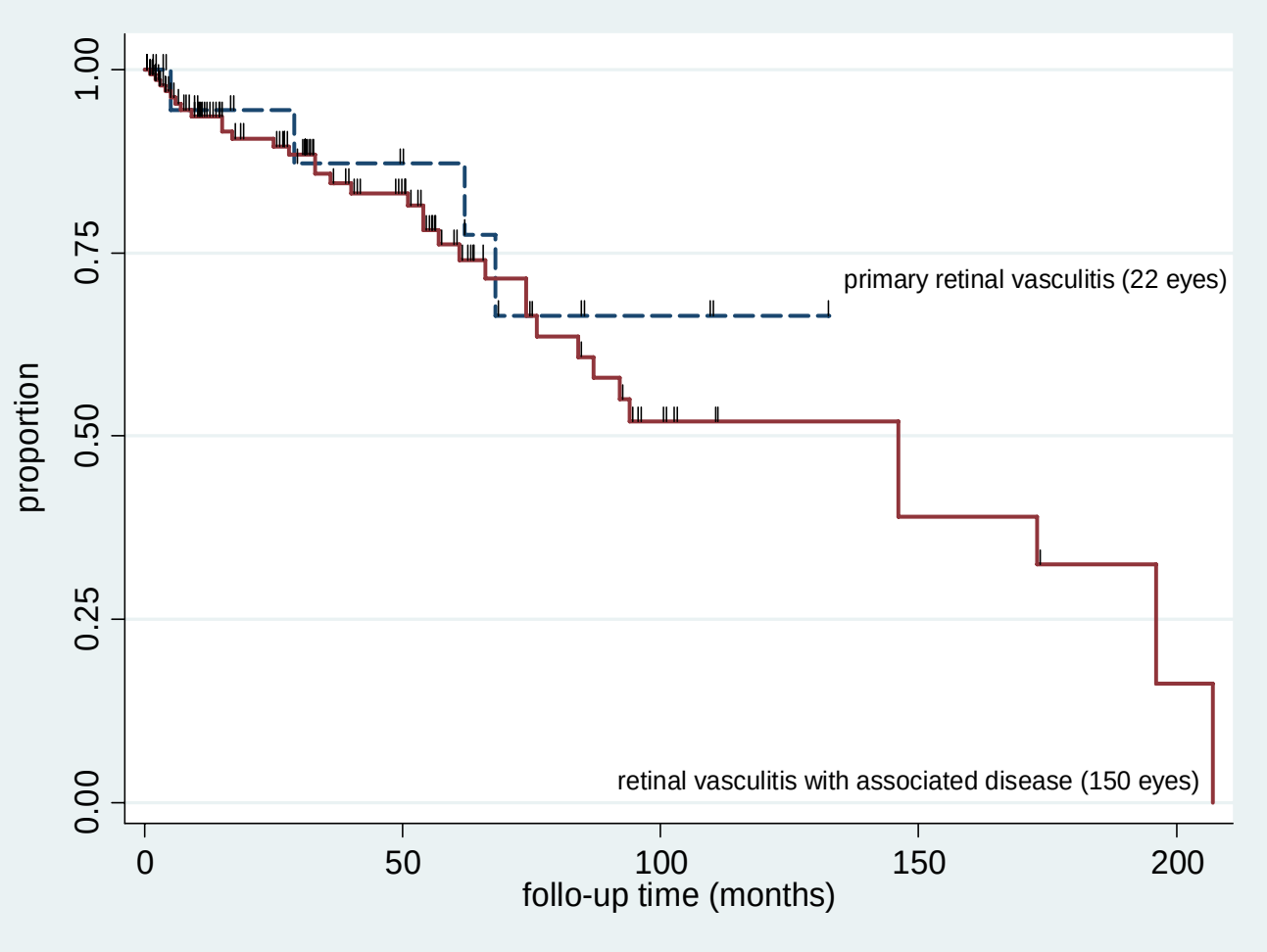
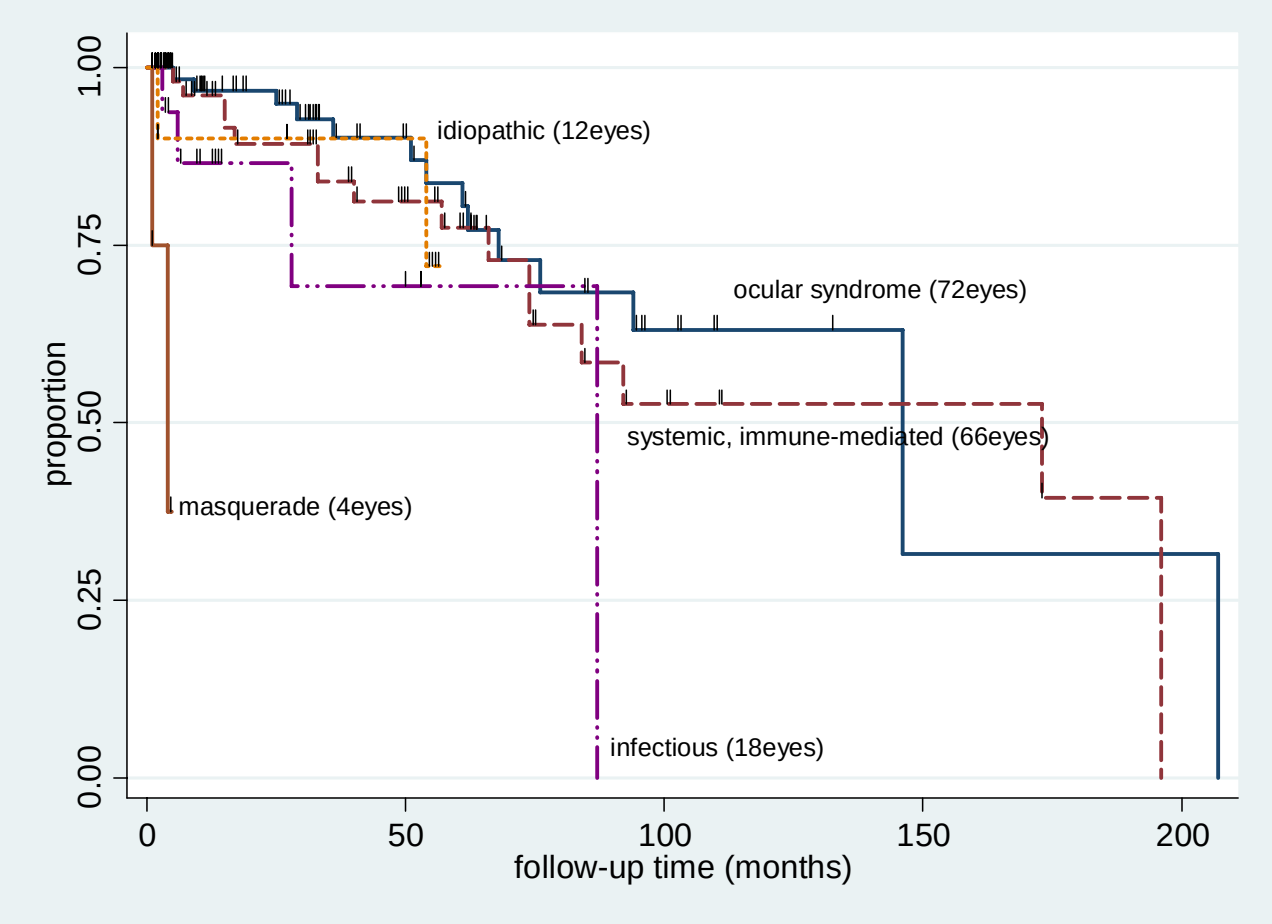


Figure 10 *Kaplan-Meier curve demonstrating the proportion of affected eyes which have not experienced vision worsening by at least 2 lines as a function of follow-up time in months (by etiologic sub-group)*



Cox proportional hazard univariate regression was performed and hazard ratios (HR) for each variable were examined in order to determine the factors predictive of vision improvement; only race (white vs. others) (HR 3.30; p <0.01; 95% CI, 1.70-6.41) and LogMAR value at baseline (HR 2.79; p<0.01; 95% CI, 1.88-4.14) were significant. Multivariate analysis using Cox proportional hazard ratio model was performed in order to evaluate whether population demographic or characteristics of uveitis are acting as covariates to influence each other in predicting the improvement probability. The length of time between disease onset and baseline

evaluation was associated with improvement (HR 0.08, p=0.02; 95% CI, 0.08-0.08). Males were more likely to improve vision (HR 3.44; p=0.005; 95% CI, 1.44-8.06). Patients with high baseline LogMAR, which corresponds to worse Snellen vision, were more likely to improve (HR 2.86; p <0.01; 95% CI, 1.77-4.64). Among the etiologic subgroups, idiopathic uveitis group was more likely to improve than any other sub-groups (HR 10.29; p<0.004; 95% CI, 2.13-49.59).

Multivariate Cox proportional hazard ratio model with shared frailty was performed to take into account the within-individual correlation (ie. correlation between the eyes within the same individual). Gender, LogMAR at baseline evaluation, and etiologic subcategories remained significant. Males were more likely to improve vision (adjusted HR 5.37;p=0.01; 95% CI, 1.46-19.76). Patients with high baseline LogMAR were more likely to improve (HR 4.58; p <0.001; 95% CI, 2.08-9.82). The idiopathic subcategory was more likely to improve than any other subcategories.

Table 9 *Univariate and multivariate Cox proportional hazard ratio model*

Variable	Univariate Cox		Multivariate Cox	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Time between onset and baseline (year)	0.08(0.08,0.08)	0.33	0.08(0.08,0.08)	0.02
Age at onset	1.0(0.98,1.02)	0.91	N/A	
Gender				
Female	reference		reference	
Male	1.74(0.90,3.37)	0.10	3.44(1.44,8.06)	<0.01
Race				
White	reference			
Others	3.30(1.70,6.41)	<0.01	N/A	
LogMAR at baseline	2.79(1.88,4.14)	<0.01	2.86(1.77,4.64)	<0.01
Laterality				
Unilateral	reference			
Bilateral	1.53(0.57,5.02)	0.48	N/A	
Etiologic sub-group				
Ocular syndrome	reference		reference	
Systemic, immune-mediated	3.06(1.29,7.29)	0.01	2.53(0.97,6.59)	0.06
Infectious	8.46(2.74,26.14)	<0.01	5.03(1.54,16.43)	0.02
Masquerade	26.09(2.81,241.49)	<0.01	6.54(0.53,81.11)	0.14
Idiopathic uveitis	4.60(1.15,18.37)	0.03	10.29(2.13,49.59)	<0.01

Table 10 *Cox shared frailty model*

Variable	HR (95% CI)	*p*-value
Gender		
Female	reference	
Male	5.37(1.46,19.76)	0.01
LogMAR at baseline	4.58(2.10,10.00)	<0.01
Etiologic sub-group		
Ocular syndrome	reference	
Systemic, immune- mediated	2.90(0.71,11.87)	0.14
Infectious	11.33(1.53,83.71)	0.02
Masquerade	5.12(0.11,231.77)	0.40
Idiopathic uveitis	12.00(1.15,124.62)	0.04

DISCUSSION

Proportion of retinal vasculitis in specific subsets of uveitis patients:

Retinal vasculitis commonly develops in association with a systemic or ocular disease (Walton & Ashmore, 2003). Graham et al. (1989) observed that among 150 retinal vasculitis patients, 67 patients had isolated retinal vasculitis, and 83 had retinal vasculitis in association with systemic inflammatory disease (Graham et al., 1989). In previous literature, Behcet's disease, sarcoidosis, and multiple sclerosis have been described as the 3 most common of systemic diseases associated with ocular vasculitis disorders (Levy-Clarke & Nussenblatt, 2005). Among these three diagnoses, Behcet's Disease has been described as the most commonly associated disease with retinal vasculitis as retinal vasculitis is seen in 66 to 73 % of all Behcet's disease cases (Charteris et al., 1992). Paovic et al. (2009) study of 1,254 uveitis patients found that primary retinal vasculitis occurred in 6.8 % in total uveitis patients, and was most commonly found (37.5%) in patients with sarcoidosis (Paovic et al., 2009). In our findings, retinal vasculitis occurred in 11% of total uveitis cases reviewed. A subset of 70 out of 677 idiopathic uveitis cases were reviewed to identify 15 retinal vasculitis patients (21.4%). When 21.4% is extrapolated assuming that retinal vasculitis occurs in the same proportion as the subset in all 677 cases, it is presumed that retinal vasculitis occurs in 14.2% in the uveitis patient population of the Uveitis clinic, and 42.3% of these cases had an identifiable systemic disease. Also, only 21.2% of the retinal vasculitis patients would have an identifiable systemic-immune mediated disease, which is much lower than the 55.3% reported in the Graham et al. (1989) study. Patients with Behcet's disease were most likely to have retinal vasculitis followed by patients with birdshot choroidopathy, acute retinal necrosis, and idiopathic uveitis with unclassifiable disease association. Retinal vasculitis was also found in very high proportions in patients with AIDS

(acquired immune deficiency syndrome) and/or cytomegalovirus (CMV), syphilis, and tuberculosis. However, the number of patients screened for each of these diagnoses constituted less than 1% of all uveitis patients reviewed and thus it is difficult to draw meaningful conclusions. Retinal vasculitis was most rarely found in patients with ankylosing spondylitis (AS), identified only in 1 out of 133 patients reviewed. Herpes simplex virus (HSV) and herpes zoster virus (HZV) are classically not classified as diagnoses associated with vasculitis, but in our findings retinal vasculitis was found in 4 patients with HSV or HZV. We speculate that this association can be explained by several reasons: (1) the association is merely a coincidence; (2) either the diagnosis of the associated disease or retinal vasculitits has been incorrectly made or ;(3) the association is atypical but a real manifestation.

We categorized the 1,307 uveitis cases reviewed based on etiology into the following sub-groups: ocular syndrome, systemic/immune-mediated, infectious, masquerade and idiopathic groups. Among these etiologic sub-categories, retinal vasculitis was most commonly found in idiopathic uveitis with unclassifiable association, followed by the ocular syndrome, infectious, and masquerade sub-groups. Retinal vasculitis was least commonly found in the systemic/immune-mediated sub-group. Of all the reviewed uveitis cases in the systemic/immune-mediated sub-group, scleritis and sarcoidosis cases predominated, together accounting for 47.7% of all cases in this group, followed by AS accounting for 16.3%. It should also be noted that scleritis is not a systemic disease but it is often associated with a systemic disease.
Classic forms of systemic vasculitides include polyarteritis, Wegener's granulomatosis, Churg Strauss and giant cell arteritis. When patients with retinal vasculitis are examined by rheumatologists, these classic systemic vasculitides would typically be considered as an underlying disease. Many of the diagnoses we have examined in this study, including sarcoidosis

and multiple scleritis are not among the entities classically considered as systemic vasculitis; we found retinal vasculitis occurring in these diseases and that retinal vasculitis is rather rare in the classic forms of systemic vasculitides.

Characteristics of the identified retinal vasculitis cases:

Graham et al. (1989) observed in their study of 150 patients with retinal vasculitis that two-thirds of the study patients were under 40 years of age. Also, retinal vasculiits was more commonly found in females (1.5:1) in the isolated retinal vasculitis group, but gender distribution was approximately equal in the cases associated with systemic disease (Graham et al., 1989). In our findings, the 178 patients identified as having retinal vasculitis, both with an underlying disease and in the isolated form, gender distribution was approximately even. The identified patients also were predominantly white, had bilateral conditions, and experienced disease onset at 37 years of age on average, occurring most frequently between 21 to 40 years.

Visual outcome of the identified retinal vasculitis cases and predictors for the outcome:

We were able to perform visual acuity analysis for the 172 eyes (98 patients) evaluated at least at two different time points. In order to ensure that the data from the 172 eyes is representative of all 269 affected eyes (178 patients), the baseline visual acuity of the 172 and the 97 eyes with only baseline visual acuity available were compared, and vision change of the 97 eyes was examined as a function of varying lengths of follow-up. No distinctive pattern was observed to raise concern regarding representativeness of the 172 eyes analyzed.

The 172 eyes with follow-up time greater than 0 months had roughly equal chances of improving or worsening by less than 2 lines, but higher chances of improving by at least 2 lines

or worsening by at least 2 lines, or not changing vision at all. Visual outcome seemed to vary by laterality of the disease and the presence of an underlying disease. Although all affected eyes studied improved on average by 2 lines per eye-year, only bilateral cases improved when stratified by laterality. This was supported by Kaplan-Meier time-to-improvement approach, which demonstrated that vision improvement was achieved in higher proportions for bilateral cases than unilateral cases. This may be due to the differences in the course of treatment the patients may have undergone depending on the laterality of the disease. Bilateral conditions often interfere with everyday life of the patient to a greater extent than unilateral conditions. It is possible that more aggressive and regular treatment may have been necessary for those with a bilateral condition, which may have led to better visual outcome.

Based on computation of Snellen visual acuity change per eye-year, primary retinal vasculitis cases and those with an underlying disease improved vision overall on average, but the rate was higher for those with primary retinal vasculitis. Examination of the Kaplan-Meier proportions of vision change revealed that vision improvement was achieved in a greater proportion for retinal vasculitis with an underlying disease compared to that in the isolated form. A greater proportion of patients with retinal vasculitis with disease association also experienced vision worsening by at least 2 lines than those with primary retinal vasculitis, which may have skewed the average change in Snellen visual acuity. Also, all patients were followed up for widely varying lengths of time. Therefore, our computation of visual acuity rate change for some patients may be an over estimate as visual acuity change observed for less than a year was assumed to be occurring at the same rate for one year in computation of vision change per eye-year.

Among the etiologic subcategories, idiopathic, systemic/immune-mediated, and infectious disease groups tended to achieve vision improvement as compared to the primary retinal vasculitis or the ocular syndrome group. It is possible that primary retinal vasculitis is more aggressive in nature and leads to worse prognosis for affected patients than the cases with an underlying disease in which retinal vasculitis may be incidental.

Our findings suggest a few factors associated with visual outcome. Gender seemed to be associated with visual outcome; males were more likely to improve vision. The duration of time between baseline evaluation and disease onset also was associated; a delay in time between disease onset and baseline evaluation was associated with worse visual outcome. Vision at baseline evaluation also seemed to be predictive of visual outcome; patients with higher logMAR, which corresponds to worse Snellen vision, were more likely to improve. Among the etiologic sub-groups, the eyes affected by uveitis with unclassifiable disease association were most likely to improve than any other sub-categories; those in the ocular syndrome subcategory were least likely to improve. When adjusted for within-individual correlations, time between disease onset and baseline evaluation was no longer significant. Gender, baseline vision, and etiologic sub-groups remained significant after adjusting for intra-individual correlation.

Limitations:

This study was a retrospective chart review study; no new information was collected directly from patients and thus data collection entirely relied on information available in past medical records. There are several limitations inherent to this approach, including data abstraction and management errors, resolving ambiguous data and management of missing data. Although all available charts were reviewed by the same reviewer, accuracy and consistency of collected data were less than could have been achieved in a prospective study. Other limitations include the controversial definition of retinal vasculitis, the absence of fluorescein angiograms on many patients, and referral-bias. In 2005, the SUN (Standardization of Uveitis Nomenclature) group attempted to define terms related to uveitis evaluation and treatment; the definition of retinal vasculitis was controversial such that no consensus has been reached. Because a standardized definition of retinal vasculitis has not been established, number of identified retinal vasculitis may vary depending on how it is being defined. The limitations in analyzing categories of retinal vasculitis should also be noted as even the diagnoses within the same sub-category could be very different. For example, even within the infectious sub-category, there are many different types of infections. Also, fluorescein angiograms were performed for only approximately 10% of all patients reviewed. Our findings may be an underestimate of the true prevalence of retinal vasculitis as fluorescein angiography is a more sensitive diagnostic tool for identifying retinal vasculitis than general ophthalmological exams. Our findings are subject to bias as disease prevalence confers significant geographical variation, and detection of retinal vasculitis may be affected by whether the patient is under the care of an ophthalmologist, a retina specialist or other medical specialists. Lastly, the uveitis clinic is a tertiary-referral center to

which more challenging cases are referred. This may have contributed to an overestimation of the true prevalence of retinal vasculitis in uveitis patients in the general population.

Strengths:

There are only a limited number of publications related to retinal vasculitis. This study is one of the first U.S. studies to examine the proportion of retinal vasculitis occurring in uveitis by disease association and etiology. This study is also the first to attempt to investigate visual outcome in patients with retinal vasculiits. To our knowledge, our study is the biggest study of retinal vasculitis patients as we examined 178 patients, and the larger sample size provides greater accuracy in ascertaining the likelihood of vision change.

Future directions:

Predicting visual outcome in patients with retinal vasculitis is often difficult as the course of the disease may vary (Standford & Verity, 2000). Visual outcome is affected by many factors such as therapy, surgical treatment, and complications such as macular ischemia. Identification of types, timing, and lengths of treatments and complications involved would be useful in developing well-established guidelines for treatment for retinal vasculitis. Also, investigating whether prognosis is affected by features of retinal vasculitis such as retinal vascular sheathing, occlusion, intraretinal hemorrhage and cotton wool spots would be valuable in predicting prognosis and for better management plan to improve chances of treatment success.

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FOOTNOTES

[1] Uveitis with unclassifiable disease association are often categorized as idiopathic uveitis in most centers