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Incidence of and Risk Factors for Cataract in Anterior Uveitis

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Purpose: To estimate the incidence/risk factors for cataract in non-infectious anterior uveitis.

Design: Retrospective multicenter cohort study (six US tertiary uveitis sites, 1978–2010).

Methods: Data were harvested by trained expert reviewers, using protocol-driven review of experts' charts. We studied cataract incidence—newly reduced visual acuity worse than 20/40 attributed to cataract; or incident cataract surgery—in 3,923 eyes of 2,567 patients with anterior uveitis.

Results: Cataract developed in 507 eyes (54/100 eye-years, 95% confidence interval (95%CI): 49–59). Time-updated risk factors associated with cataract included: older age (over 65 vs. <18 years: adjusted hazard ratio (aHR)=5.04; 95%CI, 3.04–8.33); higher anterior chamber cell grade (P(trend)=0.001), prior incisional glaucoma surgery (aHR=1.86; 95%CI, 1.10–3.14), band keratopathy (aHR=2.23; 95%CI, 1.47–3.37), posterior synechiae (aHR=3.71; 95%CI, 2.83–4.87), elevated intraocular pressure≥30 vs 6–20 mmHg: aHR=2.57; 95%CI, 1.38–4.77). Primary acute (aHR=0.59; 95%CI, 0.30–1.15) and recurrent acute (aHR=0.74; 95%CI, 0.55–0.98) had lower cataract risk than chronic anterior uveitis. Higher dose prednisolone acetate 1%-equivalent use (≥2 drops/day) was associated with >2-fold higher cataract risk in eyes with anterior chamber cell (AC) grades≤0.5+, but was not associated with higher cataract risk in the presence of ≥grade 1+ AC cells.

Conclusions: Cataract complicates anterior uveitis in ~5.4/100 eye-years. Several fixed and modifiable risk factors were identified, yielding a point system to guide cataract risk minimization. Topical corticosteroids only were associated with increased cataract risk when anterior chamber cells were absent or minimally present, suggesting their use to treat active inflammation (which itself is cataractogenic) does not cause a net increase in cataract incidence.

Introduction

Uveitis is a leading cause of visual impairment, reported to be responsible for approximately 10% of blindness worldwide.[1] Cataract development is commonly associated with uveitis, presumably because the intraocular inflammation and the most frequently implemented treatment, corticosteroids, can both induce clouding of the lens. Currently there is limited information regarding the incidence of cataract in patients with anterior uveitis and risk factors that may predispose to this complication. AlBloushi et al published a retrospective case series in patients with anterior uveitis among whom 18.3% were diagnosed with cataracts.[2] Risk factors that increased the risk of cataract included age greater than 18 years, female gender, hypopyon, and presence of posterior synechiae.[2] Korner-Stiefbold et al reviewed cases of chronic juvenile idiopathic arthritis (JIA)-associated anterior uveitis and reported that 40% developed cataract.[3] Loh and Acharya identified a 0.09/eye-year of posterior subcapsular cataracts among uveitis eyes of HLA-B27+ patients.[4] Identification of factors that would alter cataract risk could be useful both to guide clinical management and to counsel patients regarding realistic expectations of visual outcomes secondary to severity of intraocular inflammation and/or frequency of corticosteroid use.

Here we report the incidence and associated risk factors of cataract development in a large cohort of anterior uveitic eyes of patients managed at tertiary uveitis centers in the United States.

Methods:

Study design:

The Systemic Immunosuppressive Therapy for Eye Disease (SITE) Cohort Study is a multicenter retrospective cohort study that reviewed medical records of all eligible patients seen at six tertiary uveitis referral clinics in the United States beginning from center inception, yielding data spanning 1978 to 2010 inclusive. The design of the first phase of the study has been described previously;[5,6] subsequently the study was extended to include data for all eligible patients through 2010 at all six centers. Only patients with non-infectious uveitis were included in the study, and patients with HIV/AIDS were excluded. The study has maintained institutional review board approval at each of the participating centers (see Credit Roster, available in online supplement available at: http://www.ajo.com) and was conducted in accordance with the principles of the Declaration of Helsinki.

All patients in the cohort diagnosed with anterior uveitis were identified, providing the group of eyes studied in this analysis. Because of uncertainty regarding the equipotency between difluprednate 0.05% and prednisolone acetate 1%, eyes of treated with difluprednate were excluded from the analysis.

Data collection:

Information on eligible patients/eyes had been obtained from medical records generated by uveitis expert clinicians and entered into computer based standardized data entry forms by trained reviewers.[5]

Covariate data studied in this analysis included demographic characteristics of the patients, bilateral versus unilateral uveitis (whether the contralateral eye also was affected for by-eye analysis), diagnostic and clinical features of anterior uveitis (see Table 1), smoking status, other comorbidities that may increase risk of cataracts (e.g., diabetes mellitus), intraocular pressure (IOP), and use of topical and systemic medications. The study centers historically had graded anterior chamber cells in the manner subsequently advocated by the Standardization of Uveitis Nomenclature (SUN) group (most SUN leaders were founders of our participating clinics).[7] Use of all medications at every visit was recorded; use of aspirin, statins, use of non-steroidal anti-inflammatory drugs, and angiotensin converting enzyme (ACE) inhibitors were studied as potentially protective factors because we hypothesized these might affect the incidence of cataract. Time-updated variables were used: for medications and anterior chamber cells the value from the preceding visit was used up until but not including the visit where the outcome was studied, on grounds that effects would not be instantaneous and were best studied from the period just before the outcome was studied. Values were updated beginning with each succeeding visit. For clinical features representing complications of uveitis (band keratopathy and posterior synechiae), as well as prior use of periocular corticosteroid depot injections and surgeries, variables were changed from never to ever when the complication was first observed or the procedure performed.

Main Outcome Measure:

The primary objectives were to evaluate the incidence of cataract in uveitic eyes of patients with anterior uveitis in a tertiary setting, and to identify other factors that may increase the risk of developing cataract in this patient population (eg. degree of intraocular inflammation, frequency of corticosteroid eye drop use, presence of posterior synechiae). A secondary objective was to develop a “points” score system to predict cataract risk.

Cataract was defined in two ways to evaluate absolute cataract risk (the time-to-occurrence of cataract): 1) a drop in Snellen-equivalent visual acuity to a level *worse than* 20/40, which was attributed in expert clinician notes primarily on cataract; or 2) occurrence of cataract surgery. Only the first definition was used for risk factor analysis because clinicians generally control anterior chamber cells before performing cataract surgery, biasing assessment of this important variable using the cataract surgery definition.

Statistical analysis:

The incidence of cataract was summarized using a Kaplan-Meier curve with a 95% confidence interval. Potential risk factors were assessed with Cox regression using the visual acuity-based cataract outcome definition; anterior chamber inflammatory activity could not be assessed in an unbiased manner using the surgical definition because eyes typically are operated only when inflammation is suppressed. Putative predictors of cataract development were evaluated based on hazard ratios (HR) and adjusted hazard ratios (aHRs; with 95% confidence intervals [CI]), accounting for positive correlation between eyes of the same patient using the Aggregate option of PROC PHREG of SAS. A backward stepwise selection algorithm was used to identify significant risk factors for the incidence of cataract. In addition, we converted the results from the stepwise Cox regression analyses to a point system for ease of clinical use. Specifically, Beta coefficients from categories of variables

that were statistically significant were multiplied by 10 and rounded approximately to the nearest integer to obtain the point value for that category. Point values of individual variables then were summed to obtain a Total Point Score for that eye. Since there were some eye-specific predictors, the Total Point Score may differ for right and left eyes. We also generated Kaplan-Meier curves of cataract incidence for specific Total Point Score categories. All statistical analyses were performed with SAS software version 9.4 (SAS Inc., Cary, NC).

Results:

3,923 eyes of 2,567 patients were identified as having anterior uveitis: 471 (13%) with primary acute anterior uveitis (only a first episode known); 1,895 (52%) with recurrent acute anterior uveitis; and 1,277 (35%) with chronic anterior uveitis. 507 eyes (12.9%) developed visually significant cataract during follow-up; 280 (7.1%) were identified due to visual acuity worse than 20/40 attributed to cataract and 227 (5.8%) on the basis of requiring cataract surgery. Additional demographic and clinical characteristics are described in Table 1. The overall incidence of cataract was 0.054 events per eye-year (95% CI, 0.049–0.059); approximately 25% of uveitic eyes had developed cataract within three years (Figure 1).

Factors predictive of increased risk of cataract development are given in Table 2. In the final regression model, age over 65 years was associated with increased risk of incident cataract: adjusted hazard ratio (aHR)=5.04 (vs. <18 years), 95% confidence interval (CI), 3.04–8.33). Age 45–64 was associated with a lesser degree of increased risk (aHR, 2.22; 95% CI 1.43–3.44). Risk was not significantly higher at lower adult ages compared with children. Uveitic eyes of Black, non-Hispanic patients tended to have higher cataract risk than uveitic eyes of white patients (aHR, 1.38; 95% CI 0.96 – 1.98), but not to a statistically significant degree after adjusting for other factors. Anterior chamber cell grade at the prior visit worse than 0.5+ also was associated with increased cataract risk [(1+ vs. 0: aHR, 2.60; 95% CI, 1.65–4.11), (≥2+ vs. 0: aHR, 3.44; 95% CI, 2.14–5.53)]. Other risk factors included: prior incisional glaucoma surgery (aHR, 1.86; 95% CI, 1.10–3.14); presence of band keratopathy at or prior to the visit observed (aHR, 2.23; 95% CI, 1.47–3.37); presence of posterior synechiae at or prior to the visit observed (aHR, 3.71; 95% CI, 2.83–4.87); diagnosis with chronic anterior uveitis as opposed to primary acute (aHR=0.59; 95% CI, 0.30–1.15) and recurrent acute (aHR=0.74; 95% CI, 0.55–0.98) anterior uveitis; and highly elevated intraocular pressure at the preceding visit (IOP > 30 vs. 6–20 mmHg– aHR, 2.57; 95% CI, 1.38–4.77).

The use of topical corticosteroids (prednisolone acetate 1% or equipotent dose of alternative corticosteroids[8]) also was associated with increased risk of cataract development compared with non-use, with use of <2 drops daily tending to have higher hazard (aHR, 1.43; 95% CI, 0.89–2.32), and 2 drops daily or more associated with about 2-fold increased hazard (see Table 2). However, interaction testing indicated that this effect varied to a statistically significant degree across different anterior chamber cell grades. When accounting for this interaction in the final model (right columns, Table 2), use of topical corticosteroids was not associated with an additional increase in cataract incidence when the anterior cell grade was 1+ or higher. However, when minimal (grade 0.5+) or no (grade 0) uveitis activity was

present in the anterior chamber at the preceding visit, increased use of topical corticosteroids tended to be associated with greater cataract risk. For uveitic eyes with anterior cells grade 0, the incidence of cataract was significantly higher only when the dose at the preceding visit was 2 drops or more (aHR=2.18; 95% CI, 1.51–3.15). For uveitic eyes with anterior cells at grade 0.5+, the incidence of cataract tended to be higher when the preceding visit's dose was greater than 0 but less than two drops/day (aHR=2.16; 95% CI, 0.62–7.54) and was significantly higher for doses of 2 drops or more/day (aHR=2.50, 95% CI, 1.09–5.73).

Prior use of periocular corticosteroids tended to have an increased risk of cataract development (aHR 1.99; 95% CI 0.93–4.27; Table 2) but not to a statistically significant degree for this treatment which was not often used for anterior uveitis in this cohort. Use of systemic corticosteroids at the previous visit was not associated with significantly increased cataract development. Each of these two variables had a crude association with increased cataract risk, which was diminished with adjustment for anterior chamber inflammatory activity and other factors including topical corticosteroid use. Diabetes mellitus (aHR, 1.46; 95% CI, 0.97–2.21) also tended to be associated with higher risk but not to a statistically significant degree.

Factors that did not appear to alter the risk of cataract development in this uveitic population (see Table 2) included: current smoking (aHR, 1.27; 95% CI 0.85–1.88); former smoking (aHR, 1.17; 95% CI 0.77–1.79); statin use (aHR, 1.09; 95% CI 0.64–1.86); aspirin use (aHR, 0.82; 95% CI 0.46–1.49); systemic non-steroidal anti-inflammatory use (HR, 0.96; 95% CI 0.66–1.40); angiotensin converting enzyme inhibitor (ACEi) use (HR, 0.84; 95% CI 0.49–1.43). All medications were time-updated values from the previous visit.

For clinical use, the algorithm used to convert the estimates of regression coefficients from the final model in Table 2 to risk points is given in Table 3. The presence of diabetes mellitus, which had a relatively small adjusted hazard ratio which was not statistically significantly different than one, was not included in the algorithm. The points allocated to individual categories of risk factors range from 0 to 5. The Total Risk Points range at the outset of follow-up was from 0 to 12, and may differ between eyes since some items are eye-specific. We divided the Total Risk Points into three categories (0 to 2; 3 to 4; ≥5 points) and plotted the Kaplan-Meier survival curves in Figure 2. There was a substantial difference in cumulative incidence by Total Risk Points group. For example, at 5 years the estimated cumulative incidence of cataract was approximately 6% for risk points 0 to 2; 14% for risk points 3 to 4, and 38% for risk points≥5.

Discussion:

Our results indicate that visually significant cataract development is a common complication of anterior uveitis, which occurred in approximately 25% of all eyes over a 5-year period in this large retrospective cohort analysis. However, the majority of eyes do avoid cataract, especially those lacking risk factors for cataract, some of which are modifiable.

Factors that increase the risk of cataract in these patients included initial age≥65 years or 45–64 years (to a lesser degree); chronic anterior uveitis; prior incisional glaucoma surgery;

presence of band keratopathy; presence of posterior synechiae; and anterior chamber cell grade of 1+ or higher or elevated intraocular pressure≥30 mm Hg at the prior visit. Increasing age is a well-characterized risk factor for cataract.[9] Band keratopathy and posterior synechiae are associated with greater disease severity, which may contribute to increased risk of cataract. The stronger association of posterior synechiae with increased cataract risk suggests an additional mechanism may be at play, which we hypothesize to be mechanical tension on the lens itself as the iris continually moves.[10] A higher degree of anterior chamber cell as graded by SUN criteria portended a greater risk of cataract development. Those with 0.5+ anterior chamber cell grade had no significant risk of cataract; those with 1+ anterior chamber cell grade had 2.5-fold greater risk of cataract, and those with 2+ to 4+ anterior chamber cell grade had 3-fold greater risk of cataract (each with respect to grade 0).

Use of topical corticosteroids was associated with higher risk of cataract with a positive test for trend with increasing dose (see Table 2, left and middle columns). However, after adjusting for other factors, the increase in risk was less pronounced (and not significantly increased for one drop daily of prednisolone acetate 1% per day or less). Risk at higher doses leveled off at two drops daily or higher, perhaps because the corticosteroid-induced gene expression that affects cataract risk was fully mobilized. However, clinical use of topical corticosteroids is in response to higher levels of inflammation, which itself also was a risk factor for cataract[10]. Therefore, we undertook an interaction (or effect modification) analysis to evaluate the importance of these inter-related factors. The results of this analysis can be interpreted as showing that any dose of topical corticosteroids can be used without increasing cataract risk over and above that resulting from anterior chamber inflammation itself at levels of grade 1+ or higher—perhaps because the negative effects of corticosteroids on the lens are balanced by the beneficial effects on reducing inflammation. This result suggests that for induction of quiescence of anterior chamber inflammation, topical corticosteroids of any dose level do not increase the risk of cataract, and may be freely used to suppress active inflammation as quickly as possible. In eyes with minimal to no anterior chamber inflammation (grades 0 or 0.5+), topical corticosteroid use at a dose of two drops per day or more is associated with 2.2 to 2.5-fold higher risk of cataract compared with those taking no corticosteroid drops. Even one drop per day tended to have increased cataract risk, but risk was not statistically significantly increased. One drop every other day or less was not associated with increased cataract risk. These results raise the possibility that use of very low suppressive doses of topical corticosteroids may not increase the risk of cataract to a detectable degree for the average patient. However, the data suggest that suppressive topical corticosteroid therapy has the cost of higher cataract risk when a dose of two drops per day or more is used. Clinicians who elect to use a low dose suppressive approach for management of anterior uveitis nevertheless ought to monitor patients carefully for early signs of cataract, because greater susceptibility to corticosteroid-induced cataract potentially could exist in non-average patients. For non-phakic eyes, use of suppressive topical corticosteroids could be more liberal though eyes will need to be monitored for intraocular pressure elevation.[11]

Prior use of periocular corticosteroids also tended toward increased risk of cataract development, but not to a statistically significant degree. A prior study in a broader

group of uveitis cases found that use of multiple periocular injections is associated clearly with increased cataract risk,[12] suggesting that extensive use of periocular corticosteroid injections likely leads to cataract also, but one or two injections has less impact on cataract incidence. Long-term use of systemic corticosteroids clearly is associated with an increased risk of cataract in at least some patients (e.g., chronic JIA patients[3]), especially with higher doses beyond those recommended for suppressive use for uveitis treatment.[13] However, in the MUST Trial and Follow-up Study, treatment with systemic therapy which often involved long-term low-dose systemic corticosteroid therapy had relatively little cataract development.[9] Our results also suggest that systemic corticosteroids may have less cataract risk than topical corticosteroid treatments. When very low doses of topical corticosteroids are not sufficient to succeed at maintaining suppression of chronic anterior uveitis, supplemental systemic therapy[13] might allow success in controlling uveitis without much cataract risk.

We initiated this analysis anticipating that several other factors might alter the risk of cataract development. Although Black race has been associated with higher cataract risk than other American races/ethnicities in the general population,[14] we did not observe statistically significant associations amongst the races/ethnicities studied here. Prior incisional glaucoma surgery was associated with a 1.86-fold greater risk of cataract, consistent with observations in broader populations including non-uveitis patients.[15] Our study was not well-powered to assess the effects of pars plana vitrectomy, which was performed infrequently in this cohort, although it has been associated with increased risk of cataract in other settings (in some studies as high as 80% of patients requiring pars plana vitrectomy developed cataract).[16] The use of statins in the management of hyperlipidemia has been implicated in higher risk of cataract.[17] However, in our cohort, statin use was not associated with altered cataract risk. Similarly, ACE inhibitor use,[18] smoking history,[19] and diabetes mellitus[20] have been linked to cataract development previously, but these associations were not seen to a statistically significant degree in our anterior uveitis cohort. Additionally, our hypotheses that aspirin and use of non-steroidal anti-inflammatory drugs (systemically) might be associated with altered cataract risk were not supported by our data.

We developed a Point system that can be used clinically to assess cataract risk in individual eyes (Table 3), where lower numbers of points were associated with much less risk of cataract incidence (only 12% 15-year risk of cataract with 0–2 points vs 55% with five or more points). Clinicians can reduce risk by achieving favorable status of potentially modifiable risk factors (quickly controlling inflammation, preventing posterior synechiae and band keratopathy, minimizing use of topical corticosteroids when inflammation is inactive, and avoiding IOP≥30 mm Hg and need for glaucoma surgery to the extent possible—some of which may be achieved low systemic corticosteroids at doses of 7.5 mg/day or less and immunosuppressants, for instance). Minimizing risk associated with modifiable risk factors is especially important in high-risk patients (e.g., age≥65 years, after posterior synechiae and/or band keratopathy have occurred). Further validation of this scale in prospective, longitudinal studies would be valuable to confirm and refine its value. Additional data regarding use of periocular injections of corticosteroids or corticosteroid implants, which were used uncommonly for anterior uveitis in our cohort, would be valuable

to consider given that we and others have observed a higher risk of cataract with multiple periocular corticosteroid injections.[12]

The strengths of this study are the large sample size with associated increased statistical power, grading of findings by expert uveitis clinicians, and the use of quality control methods at the time of data collection to optimize the accuracy of the data. There are similarly limitations to this study that may limit applicability to a different cohort of anterior uveitis patients. All study patients received medical treatment at tertiary care facilities with physicians who specialize in inflammatory eye diseases. By the nature of these practices, our cohort may represent a greater average degree of disease severity and thus a higher risk of cataract development compared to non-tertiary populations. Similarly, this was a retrospective study with incomplete follow up and missing data, which provide limitations to assessing the true incidence of cataract if those lost and those continuing follow-up differed systematically.

Misclassification/disagreement in grading covariates and outcome between specialists likely was modest and probably unbiased in direction[21,22] (non-differential), making such misclassification unlikely to qualitatively change the results. Doses of topical corticosteroids might in some cases have varied in the interval between visits; but since our results found “effects” of two drops per day or more were similar in eyes with grade 0 or grade 0.5+ anterior chambers cells, it is unlikely that enough were misclassified across this threshold to qualitatively alter results. For the purposes of this analysis, it was assumed that the use of topical corticosteroid eye drops was referring to prednisolone acetate 1% or a bioequivalent dose of an alternative topical corticosteroid. In 2008, the United States Food and Drug Administration approved difluprednate 0.05% for the treatment of post-operative inflammation and uveitis. This entity is more potent than prednisolone acetate 1%[23] and may pose greater risk for cataractogenesis,[24] especially with maintenance therapy at doses of more than one drop every other day. We were not fully able to establish equipotency for this drug, so we excluded eyes treated with it from our analysis.

In summary, the incidence of cataract in eyes with anterior uveitis is considerable but not universal. The factors that portend greater risk for cataract development include higher age, higher anterior chamber cell grade, chronic as opposed to remitting anterior uveitis, prior incisional glaucoma surgery, presence of band keratopathy, presence of posterior synechiae, and elevated IOP≥30 mmHg. Some of these factors are avoidable or could be prevented in some cases coming under care at an early enough stage. Use of doses of prednisolone acetate 1% of 2 drops per day or more was associated with higher risk of cataract in quiet or mostly quiet eyes, but when a greater degree of inflammation was present, the dose of topical corticosteroids did not affect cataract risk. These results suggest that high dose topical corticosteroids can be used freely for induction therapy (controlling active inflammation) but that topical corticosteroids need to be minimized for maintenance/suppressive therapy as much as possible in non-cataractous eyes, e.g., by using supplementary systemic therapy when activity cannot be suppressed with prednisolone acetate 1% one drop per day or preferably less. If suppressive topical corticosteroid therapy is contemplated, eyes should be monitored for early signs of cataract and treatment adjusted accordingly, as not all eyes may respond in an average way. Consistently maintaining good

control of uveitis with prevention of posterior synechiae, band keratopathy, and the need for glaucoma surgery while minimizing use of local corticosteroid therapy—e.g., with systemic therapies—are strategies that could be valuable to reduce cataract risk in phakic eyes with anterior uveitis. The point system we propose, which could be used by clinicians in deciding how to apply this information on a case-by-case basis, will benefit from further validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table of Contents Statement

Among 3,923 tertiary-managed anterior uveitic eyes, cataract incidence was 54/100eye-years. Risk factors included old age, higher recent anterior chamber cell-grade (AC), prior incisional glaucoma surgery, band keratopathy, posterior synechiae, currently elevated intraocular pressure≥30mmHg, and chronic vs acute-remitting anterior uveitis. In active eyes (AC≥1+), cataract risk was unassociated with topical corticosteroid dosage, supporting use of high doses to suppress uveitis activity. When AC≤0.5+, prednisolone acetate 1%-equivalent≥2 drops/day increased cataract incidence>2-fold; but≤1 drop/day was unassociated with cataract.

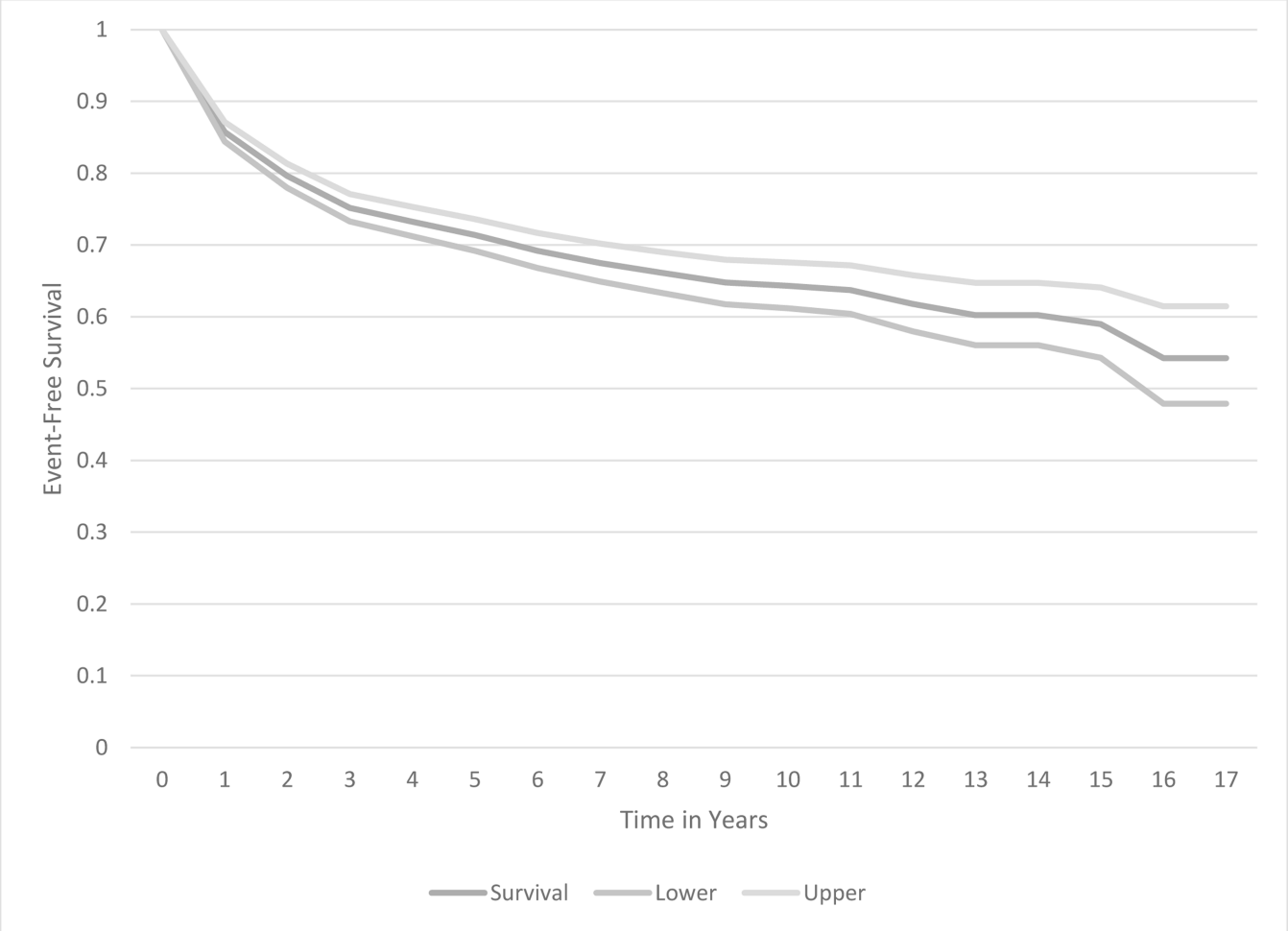

Figure 1:

Cataract-free survival with 95% Confidence Limits, among eyes with anterior uveitis from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study. The overall incidence of cataract (the first-occurring of cataract surgery or reduction in visual acuity worse than 20/40 primarily attributed to cataract) was 0.054/eye-year, 95% confidence interval, 0.049–0.059.

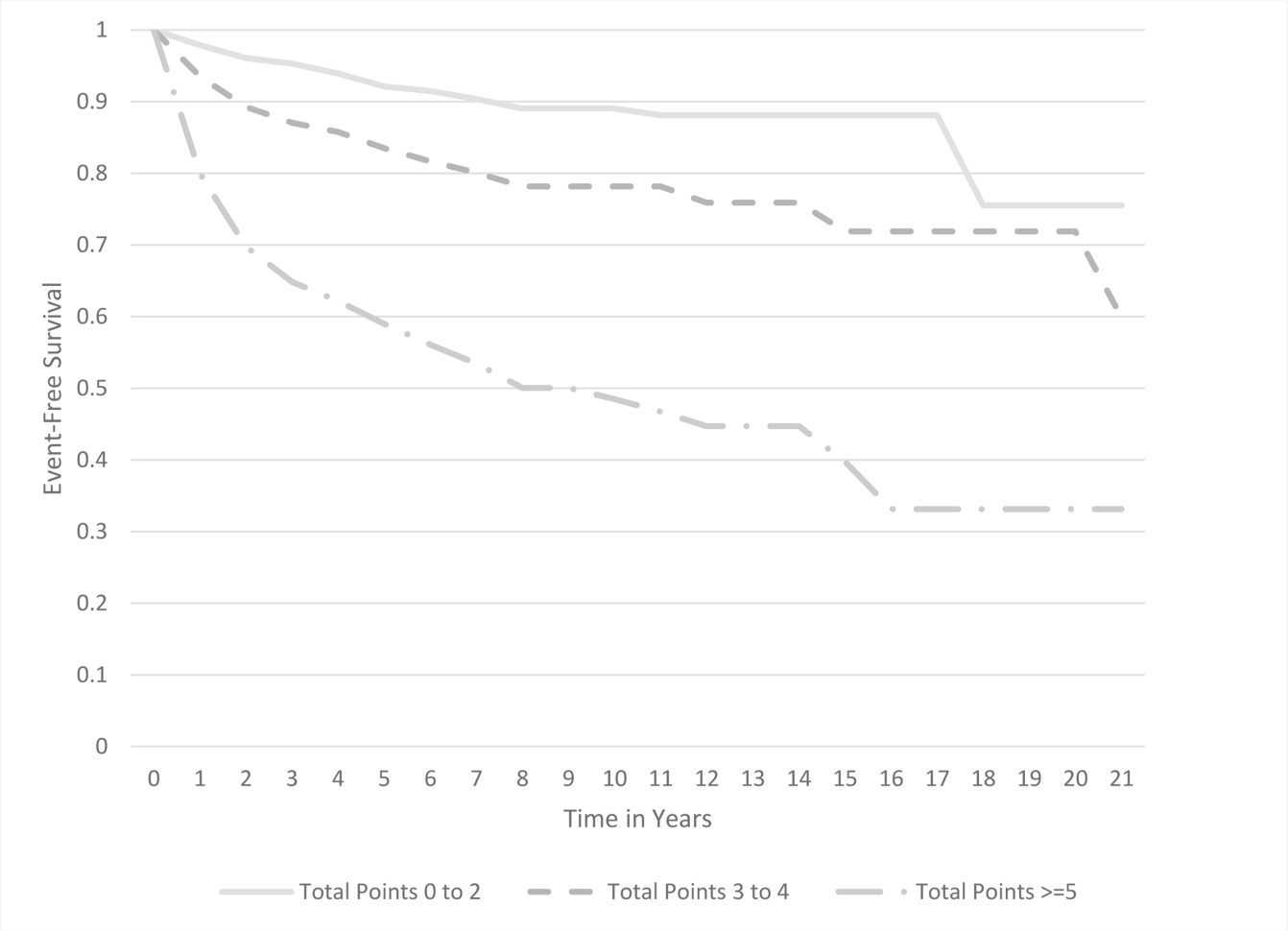

Figure 2:

Cataract-free survival by Total Points Group, among eyes with anterior uveitis from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study. At 5 years, the estimated cumulative incidence of cataract was approximately 6% for risk points 0 to 2; 14% for risk points 3 to 4, and 38% for risk points≥5. At 15 years, the estimated cumulative incidence of cataract was approximately 12% for risk points 0 to 2; 24% for risk points 3 to 4, and 55% for risk points≥5.

Table 1

Initial Characteristics of Eyes With Anterior Uveitis At Risk of Cataract

	Right Eye	Left Eye	All Involved Eyes
	N=1822	N=1821	N=3643
	N (%)	N (%)	N(%)
Characteristics of participants			
Age at day 0, years			
< 18	248 (14)	240 (13)	
18–29	207 (11)	226 (12)	
30–44	577 (32)	584 (32)	
45–64	631 (35)	615 (34)	
65+	159 (9)	156 (9)	
Gender			
Male	670 (37)	678 (37)	
Female	1152 (63)	1143 (63)	
Race/Ethnicity			
White	1204 (66)	1214 (67)	
Black	227 (12)	234 (13)	
Hispanic (Any Race)	91 (5)	79 (4)	
Other	300 (16)	294 (16)	
Diabetes			
No	1694 (93)	1688 (93)	
Yes	128 (7)	133 (7)	
Smoker			
Never	1390 (76)	1382 (76)	
Former	186 (10)	187 (10)	
Current	246 (14)	252 (14)	
Potentially Protective Medications			
Aspirin			
Never	1727 (95)	1733 (95)	
Ever	95 (5)	88 (5)	
Statin			
Never	1707 (94)	1704 (94)	
Ever	115 (6)	117 (6)	
NSAID			
Never	1523 (84)	1516 (83)	
Ever	299 (16)	305 (17)	
ACE Inhibitor			
Never	1727 (95)	1733 (95)	
Ever	95 (5)	88 (5)	

	Right Eye	Left Eye	All Involved Eyes
	N=1822	N=1821	N=3643
	N (%)	N (%)	N(%)
Characteristics of Eyes			
Anterior Chamber Cell Grade			
Quiet	874 (48)	870 (48)	1744 (48)
0.5+	347 (19)	324 (18)	671 (18)
1+	251 (14)	256 (14)	507 (14)
2+	188 (10)	222 (12)	410 11)
3+	129 (7)	115 (6)	244 (7)
4+	33 (2)	34 (2)	67 (2)
All Anterior Uveitis			
Primary Acute Anterior Uveitis	228 (13)	243 (13)	471 (13)
Recurrent Acute Anterior Uveitis	950 (52)	945 (52)	1895 (52)
Chronic Anterior Uveitis	644 (35)	633 (35)	1277 (35)
Bilateral Disease			
Ever	1408 (77)	1415 (78)	2823 (77)
Never	414 (23)	406 (22)	820 (23)
Prior Vitrectomy Surgery			
Ever	4 (0.2)	7 (0.3)	11 (.2)
Never	2244 (100)	2238 (100)	4482 (100)
Prior Incisional Glaucoma Surgery			
Ever	27 (1)	31 (2)	58 (2)
Never	1795 (99)	1790 (98)	3585 (98)
Band Keratopathy			
Ever	59 (3)	71 (4)	130 (4)
Never	1763 (97)	1750 (96)	3513 (96)
Posterior Synechiae			
Ever	415 (23)	430 (24)	845 (23)
Never	1407 (77)	1391 (76)	2798 (77)
IOP			
< 6	15 (1)	14 (1)	29 (1)
6 – 20	1569 (86)	1549 (85)	3118 (86)
21 – 29	188 (10)	204 (11)	392 (11)
≥ 30	50 (3)	54 (3)	104 (3)
Prior periocular corticosteroid injection			
None	1758 (96)	1756 (96)	3514 (96)
Some	64 (4)	65 (4)	129 (4)
Systemic Corticosteroid			
None	1626 (89)	1611 (88)	3237 (89)

	Right Eye	Left Eye	All Involved Eyes
	N=1822	N=1821	N=3643
	N (%)	N (%)	N(%)
≤7.5mg/day	33 (2)	42 (2)	75 (2)
>7.5 mg/day	163 (9)	168 (9)	331 (9)
Topical Corticosteroids			
None	711 (39)	723 (40)	1434 (39)
1 drop	128 (7)	134 (7)	262 (7)
2 drops	141 (8)	141 (8)	282 (8)
3 drops	125 (7)	117 (6)	242 (7)
4 drops	210 (12)	194 (1)	404 (11)
5–8 drops	238 (13)	248 (14)	486 (13)
> 8 drops	269 (15)	264 (15)	533 (15)

Table 2:

Factors Associated with Incident Cataract in Eyes with Anterior Uveitis, SITE Cohort Study *

	Crude Associations (Unadjusted)		Multivariate Adjusted Model (Adjusted for All Covariates)		Final Model: (Adjusted for Stepwise-Backward Selected Covariates)	
	N=280 patients 29,316 visits		N=280 patients 29,316 visits		N=280 Patients 29,316 visits	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age at day 0, years						
< 18	Ref		Ref		Ref	
18–29	1.10 (0.64 – 1.89)	0.718	1.29 (0.74 – 2.26)	0.375	1.37 (0.78 – 2.39)	0.28
30–44	0.78 (0.50 – 1.22)	0.277	1.17 (0.74 – 1.88)	0.502	1.21 (0.77 – 1.92)	0.41
45–64	1.36 (0.90 – 2.05)	0.143	2.16 (1.36 – 3.42)	0.001	2.22 (1.43 – 3.44)	0.0004
65+	3.24 (2.04 – 2.14)	<0.0001	4.95 (2.90 – 8.43)	<0.0001	5.04 (3.04 – 8.33)	<.0001
P-Trend		*<0.0001*				
Sex						
Female	Ref		Ref			
Male	0.88 (0.67 – 1.17)	0.387	0.88 (0.65 – 1.18)	0.381		
Race/Ethnicity						
White	Ref		Ref			
Black	1.49 (1.04 – 2.14)	0.031	1.38 (0.96 – 1.98)	0.083		
Hispanic	1.11 (0.61 – 2.03)	0.725	1.00 (0.51 – 1.95)	0.997		
Other	0.88 (0.59 – 1.31)	0.523	1.09 (0.71 – 1.68)	0.690		
P-Heterogeneity		*0.139*		*0.466*		
Diabetes mellitus						
No	Ref		Ref		Ref	
Yes	1.45 (0.96 – 2.18)	0.076	1.42 (0.91 – 2.22)	0.120	1.46 (0.97 – 2.21)	0.07
Smoking						
Never	Ref		Ref			
Former	1.22 (0.82 – 1.83)	0.332	1.17 (0.77 – 1.79)	0.458		
Current	1.64 (1.14 – 2.36)	0.007	1.27 (0.85 – 1.88)	0.245		
P-Heterogeneity		*0.097*		*0.493*		
AC Cells (time-updated, value at preceding visit)						
Quiet	Ref		Ref		Ref	
0.5+	1.54 (1.09 – 2.17)	0.015	1.05 (0.73 – 1.51)	0.812	0.88 (0.40 – 1.93)	0.74
1+	2.41 (1.63 – 3.57)	<0.0001	1.52 (0.98 – 2.37)	0.064	2.60 (1.65 – 4.11)	<.0001
2+, 3+, 4+	3.16 (2.09 – 4.78)	<0.0001	1.93 (1.21 – 3.09)	0.006	3.44 (2.14 – 5.53)	<.0001

	Crude Associations (Unadjusted)		Multivariate Adjusted Model (Adjusted for All Covariates)		Final Model: (Adjusted for Stepwise-Backward Selected Covariates)	
	N=280 patients 29,316 visits		N=280 patients 29,316 visits		N=280 Patients 29,316 visits	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
P-Trend		*<0.0001*		*0.001*		
Type of Anterior Uveitis						
Chronic Anterior Uveitis	Ref		Ref		Ref	
Primary Anterior Uveitis	0.44 (0.23 – 0.83)	0.012	0.60 (0.30 – 1.18)	0.136	0.59 (0.30 – 1.15)	0.12
Recurrent Anterior Uveitis	0.54 (0.41 – 0.71)	<0.0001	0.77 (0.57 – 1.04)	0.085	0.74 (0.55 – 0.98)	0.04
P-Heterogeneity		*<0.0001*		*0.032*		
Bilaterality of Uveitis						
Never	Ref		Ref			
Ever	0.91 (0.67 – 1.25)	0.570	0.97 (0.70 – 1.35)	0.865		
Prior Incisional Glaucoma Surgery						
Never	Ref		Ref		Ref	
Ever	3.03 (1.94 – 4.72)	<0.0001	1.83 (1.08 – 3.10)	0.026	1.86 (1.10 – 3.14)	0.02
Band Keratopathy						
Never	Ref		Ref		Ref	
Ever	3.47 (2.35 – 5.12)	<0.0001	2.20 (1.44 – 3.36)	0.0003	2.23 (1.47 – 3.37)	0.0001
Posterior Synechiae						
Never	Ref		Ref		Ref	
Ever	4.98 (3.82 – 6.50)	<0.0001	3.72 (2.81 – 4.93)	<0.0001	3.71 (2.83 – 4.87)	<.0001
IOP (time-updated), mmHg						
< 6	2.71 (0.98 – 7.46)	0.054	1.28 (0.46 – 3.56)	0.635		
6 – 20	Ref		Ref		Ref	
21 – 29	1.33 (0.87 – 2.01)	0.185	1.01 (0.64 – 1.61)	0.959		
≥ 30	3.98 (2.32 – 6.82)	<0.0001	2.78 (1.52 – 5.08)	0.0009	2.57 (1.38 – 4.77)	0.003
P-Trend		*0.0003*		*0.035*		
Topical Corticosteroids ((prednisolone acetate 1% or equipotent dose of alternative, time-updated)						
None	Ref		Ref			
1 drop	1.61 (1.00 – 2.61)	0.052	1.43 (0.89 – 2.32)	0.143		
2 drops	2.93 (1.90 – 4.50)	<0.0001	2.04 (1.30 – 3.20)	0.002		
3 drops	3.22 (1.91 – 5.42)	<0.0001	2.19 (1.27 – 3.80)	0.005		
4 drops	2.64 (1.69 – 4.14)	<0.0001	1.61 (0.99 – 2.63)	0.058		
5–8 drops	3.11 (2.05 – 4.73)	<0.0001	1.94 (1.23 – 3.04)	0.004		
> 8 drops	3.46 (2.24 – 5.36)	<0.0001	1.84 (1.11 – 3.05)	0.018		

	Crude Associations (Unadjusted)		Multivariate Adjusted Model (Adjusted for All Covariates)		Final Model: (Adjusted for Stepwise-Backward Selected Covariates)	
	N=280 patients 29,316 visits		N=280 patients 29,316 visits		N=280 Patients 29,316 visits	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
P-Trend		*<0.0001*		*0.009*		
Prior periocular corticosteroid injection						
None	Ref		Ref			
Ever (1 or more)	4.11 (1.97 – 8.58)	0.0002	1.99 (0.93 – 4.27)	0.076		
Systemic Corticosteroid (prednisone or equipotent dose of alternative, time-updated)						
None	Ref		Ref			
≤ 7.5mg/day	2.21 (1.32 – 3.71)	0.003	1.49 (0.83 – 2.68)	0.187		
< 7.5 mg/day	1.89 (1.27 – 2.82)	0.002	1.32 (0.87 – 2.01)	0.196		
P-Heterogeneity		*0.0007*		*0.208*		
Aspirin						
Never	Ref		Ref			
Ever	0.73 (0.41 – 1.31)	0.29	0.82 (0.46 – 1.49)	0.517		
Statin						
Never	Ref		Ref			
Ever	1.15 (0.73 – 1.82)	0.541	1.09 (0.64 – 1.86)	0.753		
NSAID						
Never	Ref		Ref			
Ever	0.85 (0.60 – 1.21)	0.36	0.96 (0.66 – 1.40)	0.838		
ACE Inhibitor						
Never	Ref		Ref			
Ever	0.91 (0.52 – 1.58)	0.737	0.84 (0.49 – 1.43)	0.522		
Prior Vitrectomy Surgery						
Never	Ref		Ref			
Ever	0.79 (0.11 – 547)	0.812	0.32 (0.04 – 2.53)	0.282		
Topical Corticosteroid Eyedrop Use When Anterior Chamber Cell Grade=0, Time-Updated						
				AC=0; Drops=0	Ref	
				AC=0; Drops=>0 and<2/day	1.35 (0.77 – 2.38)	0.30
				AC=0; Drops≥2/day	(1.51 – 3.15)	<0.0001
Topical Corticosteroid Eyedrop Use When Anterior Chamber Cell Grade=0.5+, Time-Updated						
				AC=0.5+; Drops=0	Ref	
				AC=0.5+; Drops≥0 and<2/day	2.16 (0.62 – 7.54)	0.23
				AC=0.5+; Drops≥2/day	2.50 (1.09 – 5.73)	0.03

*Incidence of Cataract (defined as visual acuity worse then 20/40 attributed to cataract); SITE=Systemic Immunosuppression for Eye Diseases Cohort Study. HR=hazard ratio; CI=confidence interval; Ref=reference group; AC Cells=grade of anterior chamber inflammatory cells; IOP=intraocular pressure. Topical corticosteroid doses refer to the dose of prednisolone acetate 1% or a dose of an alternative topical corticosteroid bioequivalent to the given dose as if it were prednisolone acetate 1% (see text). Variables marked Ever/Never are counted as never exposed until the first visit at which exposure was noted, and from that point are counted as ever exposed. Multivariate adjusted values (middle columns) also are adjusted for variables omitted above due to non-association (use of aspirin, statins, NSAIDS (non-steroidal anti-inflammatory drugs), angiotensin converting enzyme inhibitors) or small numbers (prior vitrectomy). The right columns give the final model including the interaction variables at the bottom (see text); diabetes mellitus was selected for the model using the SAS procedure, but was not significantly associated with the outcome using Wald testing.

Table 3:

Derivation of Risk Points to predict incidence of cataract, eyes with anterior uveitis, SITE Cohort Study*

	Risk Points		Risk Points		Risk Points
Age at day 0, years		**Band Keratopathy**		**AC cell grade/topical CS drop dose (interaction)**	
< 18	0	Ever Present	2	AC=0; Drops=0	0
18–29	0	Never Present	0	AC=0; Drops=1	0
30–44	0			AC=0; Drops≥2	2
45–64	2	**Posterior Synechiae**			
65+	5	Ever Present	3	AC=0.5+; Drops=0	0
		Never Present	0	AC=0.5+; Drops=1/day	0
Type of Anterior Uveitis				AC=0.5+; Drops≥2/day	2
Primary Anterior Uveitis	0	**IOP** (time-updated), mmHg			
Recurrent Anterior Uveitis	0	< 6	0	AC=0.5+	0
Chronic Anterior Uveitis	1	6 – 20	0	AC=1+	2
		21 – 29	0	AC=2+,3+,4+	3
Prior Incisional Glaucoma Surgery		≥ 30	2		
Ever	1				
Never	0				

*Values are adapted from the Hazard Ratios from the final model in Table 2. SITE=Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; IOP=intraocular pressure, AC=anterior chamber cell grade; Drops: 1/day=between more than zero and less than two per day, prednisolone acetate 1% or equipotent dose of alternative topical corticosteroid drop (eyes treated with difluprednate eye drops were excluded from entire analysis)