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Risk of Ocular Hypertension in Adults with Non-infectious Uveitis

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Abstract

Objective—To describe the risk and risk factors for ocular hypertension (OHT) in adults with non-infectious uveitis.

Design—Retrospective, multicenter, cohort study.

Participants—Patients aged ≥ 18 years with non-infectious uveitis seen between 1979 and 2007 at 5 tertiary uveitis clinics.

Methods—Demographic, ocular and treatment data were extracted from medical records of uveitis cases.

Main outcome measures—Prevalent and incident OHT with intraocular pressures (IOP) of ≥ 21 mmHg, ≥ 30mmHg and rise of ≥ 10 mmHg from documented IOP recordings (or use of treatment for OHT).

Results—Among 5270 uveitic eyes of 3308 patients followed for OHT, the mean annual incidence rates for OHT ≥ 21mmHg and OHT ≥ 30mmHg are 14.4% (95%CI: 13.4%, 15.5%) and 5.1% (95% CI: 4.7%, 5.6%) per year, respectively. Statistically significant risk factors for incident OHT ≥ 30mmHg included: systemic hypertension (adjusted hazard ratio (aHR) = 1.29); worse presenting visual acuity (20/200 or worse vs 20/40 or better, aHR = 1.47); pars plana vitrectomy (aHR = 1.87); prior history of OHT in the other eye: IOP ≥ 21 mmHg (aHR = 2.68), ≥ 30 mmHg (aHR=4.86), and prior/current use of IOP-lowering drops or surgery in the other eye (aHR = 4.17); anterior chamber cells: 1+ (aHR = 1.43) and ≥ 2+ (aHR = 1.59) vs none; epiretinal membrane (aHR=1.25); peripheral anterior synechiae (aHR = 1.81); current use of prednisone >7.5 mg/day (aHR = 1.86); periocular corticosteroids in the last three months (aHR = 2.23); current topical corticosteroid use [≥ 8X/day vs. none] (aHR=2.58); and prior use of fluocinolone acetonide implants (aHR = 9.75). Bilateral uveitis (aHR = 0.69) and previous hypotony (aHR=0.43) were associated with statistically significantly lower risk of OHT.

Conclusions—OHT is sufficiently common in eyes treated for uveitis that surveillance for OHT is essential at all visits for all cases. Patients with one or more of the several risk factors identified are at particularly high risk, and must be carefully managed. Modifiable risk factors, such as use of corticosteroids, suggest opportunities to reduce OHT risk, within the constraints of the overriding need to control the primary ocular inflammatory disease.

Elevated intraocular pressure (IOP) or ocular hypertension (OHT) in uveitis is commonly attributed to resistance to aqueous outflow related to trabecular meshwork exposure to filtered inflammatory cells, cytokines, iris pigment, corticosteroids, or possibly other factors.¹ OHT can lead to glaucoma with optic nerve damage; therefore understanding the risk and predictors of OHT is of great clinical importance.^{2–4} OHT and glaucoma are common in severe cases of uveitis, such as those enrolled in the Multicenter Uveitis Steroid Treatment (MUST) Trial, where 24% of uveitic eyes that manifested an IOP rise by 10 mmHg or more developed glaucomatous optic neuropathy within 2 years.⁵ Fluctuation in

intraocular pressure is known to increase the trabecular meshwork extracellular matrix and may additionally compromise an eye with uveitis, increasing the risk of glaucoma.⁶ The corticosteroid therapy used as the mainstay for quelling active intraocular inflammation is associated with a higher incidence of OHT, although the extent of risk with various corticosteroid therapeutic approaches requires further clarification, especially over longer follow-up times.^{7–10} Friedman et al have reported that fluocinolone acetonide implant therapy is associated with a 4-fold risk of developing IOP elevation of 10 mmHg and of incident glaucomatous optic neuropathy compared with systemic anti-inflammatory therapy.⁵

OHT is considered the most important risk factor for glaucoma; lowering IOP is the main strategy for preventing glaucoma in patients who are at risk and for slowing progression in those with established glaucoma.^{11–13} However, management of uveitic glaucoma is particularly challenging as the treatment aims both to reduce inflammation and to lower intraocular pressure, objectives which may be at odds. The success of glaucoma surgery is decreased in eyes with uveitic glaucoma, and surgical interventions are associated with a higher incidence of postoperative complications,^{14–17} which entails a further management challenge.

In order to better characterize the risk of OHT, and its risk factors, we assessed the prevalence and incidence among adult uveitis patients in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study, a large retrospective cohort study of cases of non-infectious inflammatory eye diseases.^{18,19}

METHODS

The study was conducted in accordance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The institutional review boards of each of the participating tertiary uveitis centers approved the retrospective study methods, including waiver of informed consent. SITE was registered as a cohort study (<http://www.clinicaltrials.gov> (identifier, NCT00116090; June 26, 2005)).

Study Population

The design and methods used in the SITE Cohort Study have been described elsewhere.^{18,19} In brief, cases of non-infectious ocular inflammation not known to have HIV infection who presented to the study centers during the study period were evaluated using retrospective chart review. For this report, all children <18 years upon entry into the cohort were excluded, as they have been reported separately.²⁰ Data were extracted from the case records of the patients seen between January 1978 and December 2007 from 5 specialty uveitis centers. All adults who had been diagnosed as having any form of uveitis as the primary inflammatory eye disease at presentation were included.

Data Collection

Data collection was performed by trained, certified, expert reviewers who reviewed the medical charts of the eligible patients and input information into a custom Microsoft Access

Database (Microsoft Corporation, Redmond, WA). Data included demographic characteristics at baseline, ocular and treatment characteristics for each eye at each visit.

Main Outcome Measures

Intraocular pressure was recorded for each eye during each follow up visit, as it had been measured for clinical care. Use of medications to treat OHT also was recorded. The prevalence of ocular hypertension (OHT, at the levels of an IOP ≥ 21 mmHg, and IOP ≥ 30 mmHg; or use of IOP-lowering medications; or prior IOP-lowering surgery) at the first clinic visit and the incidence of OHT among those without prevalent OHT during follow up (IOP ≥ 21 mmHg, IOP ≥ 30 mmHg, and/or a rise in IOP from the first visit by ≥ 10 mmHg; or new use of IOP-lowering medications; or new IOP-lowering surgery) were assessed. To avoid missing events when cases presented taking IOP-lowering therapy or started IOP-lowering therapy in the interval between uveitis clinic visits, cases taking IOP-lowering therapy (or post IOP-lowering surgery) at a given visit were counted as having the respective events at that point of observation. Incidence rates of and risk factors for the development of OHT were primary outcome measures. The three categories of incident OHT were analyzed separately. All outcomes were assessed at each available follow up visit. Incident IOP elevation was counted as an event upon observation at a single visit without a requirement that IOP elevation be sustained (which was not feasible with the use of time-varying covariate).

The following variables were assessed for their potential association with all three categories of OHT: (1) demographic and habit characteristics such as age, gender, race and smoking characteristics; (2) systemic diseases such as systemic hypertension, diabetes mellitus, hyperlipidemia, sarcoidosis, juvenile idiopathic arthritis, spondyloarthritis and Behçet Disease; (3) duration and type of uveitis; (4) ocular inflammatory signs such as overall inflammatory activity, anterior chamber cell grade, vitreous cell grade, vitreous haze grade, hypopyon; keratic precipitates, chorioretinal lesions, snowballs, vascular occlusions, epiretinal membrane band keratopathy, posterior synechiae, and peripheral anterior synechiae; (5) OHT in the opposite eye; (6) systemic, oral, topical, periocular, intraocular corticosteroids and corticosteroid implants (For intraocular/periocular injection to be counted a limit of 30 days was used); (7) other anti-inflammatory drugs and biologics. Variables that change over time such as ocular inflammatory signs, OHT in the contralateral eye, and treatment status were evaluated as time-varying covariates. For these variables, the values at the same time as the outcome of interest was assessed were used.²¹ For depot corticosteroid injections (periocular or intravitreal), medication was assumed to be present for three months after the injection.^{22,23}

Statistical Analyses

Eye-specific data were used for this analysis. OHT prevalence was evaluated as the proportion meeting each outcome definition at the first visit; risk factor analysis was based on crude and adjusted odds ratios (ORs) for covariates of interest calculated using logistic regression that incorporated generalizations of generalized estimating equations to account for correlation between the eyes of individual patients.

OHT incidence was evaluated based on the number of events per eye-year at risk, with observation beginning at the time of cohort entry; risk factor analysis was based on crude and adjusted hazard ratios (HRs) for covariates of interest calculated using Cox proportional hazards models with a robust sandwich estimate to account for correlation between the eyes of individual patients. Individual strata could not be evaluated using a Kaplan-Meier approach for time-varying variables, therefore the overall cumulative incidence and the assumption of proportionality between strata were utilized to calculate strata-specific cumulative incidence. This was done for all variables, including those that are time-invariant. This approach allowed estimation of nonlinear ocular hypertension rates and confidence intervals consistent with the hazard ratios while accounting for correlation between eyes of the same patient.

Each OHT outcome (≥ 21 mmHg and ≥ 30 mmHg for prevalence and incidence, and $\geq +10$ mmHg for incidence) was modeled independently, and 95% confidence intervals (CIs) were provided for all point estimates. *P* values were nominal and 2-sided. To select characteristics included in all adjusted logistic regression (prevalence) and Cox proportional hazards (incidence) models, a backward stepwise selection process was used simultaneously in the respective IOP ≥ 30 models, where characteristics with $p > 0.05$ in both models were stepwise excluded, and those remaining were adjusted for in all five models (so as to adjust for the same covariates in all multiple regressions). Intraocular and periocular corticosteroid use within the last three months also were retained in the Cox models despite not having enough data at baseline to test them in the logistic regression models. All statistical analyses were performed with SAS software version 9.4 (SAS Inc., Cary, NC).^{24,25}

RESULTS

Prevalence of Intraocular Pressure Elevation at Presentation

Among 11,452 uveitic eyes (of 7,062 patients), 290 (2.5%) eyes had OHT ≥ 30 mmHg and 1,525 (13.3%) eyes had OHT ≥ 21 mmHg at cohort entry. The highest prevalence of OHT ≥ 21 mmHg was in eyes with panuveitis ($n=204$, 16.0%) followed by anterior uveitis ($n=771$, 14.6%), intermediate uveitis ($n=296$, 11.3%) and posterior uveitis ($n=254$, 11.3%; overall $p < 0.001$). In addition, among all eyes at cohort entry, a total of 269 (2.4%) eyes with uveitis had undergone anti-glaucoma surgery before cohort entry and 1,482 (13.0%) were on anti-glaucoma medication at cohort entry.

Risk Factors for Ocular Hypertension at Presentation

The distribution of demographic, ocular, systemic and treatment covariates at presentation, as well as the significant crude and adjusted odds ratios (aOR) for the prevalence of OHT ≥ 21 mmHg and OHT ≥ 30 mmHg at presentation are summarized in an abridged form highlighting important findings in Table 1, and a complete form in Table 2 (available at <http://aojournal.org>). OHT ≥ 21 mmHg and OHT ≥ 30 mmHg at presentation had similar patterns of association. For simplicity, only results for OHT ≥ 30 mmHg at presentation are summarized here in the text.

OHT 30 mmHg at presentation was associated with age, gender and race to a statistically significant degree. Those 65 years of age and above had an increased risk of elevated OHT 30 mmHg at presentation (aOR=1.25, 95% CI 1.04–1.51) when compared with patients aged 45–64 years. Younger adults between 18–29 years (aOR= 0.63, 95% CI 0.51–0.77) and between 30–44 years (aOR=0.70, 95% CI 0.60–0.81) had a lower risk than patients aged 45–64 years. Females had lower risk (aOR=0.75, 95% CI 0.66–0.85) than males. After adjusting for other factors, eyes of white, black and Hispanic persons had similar risk, whereas those of other races/ethnicities had a higher risk (aOR=1.32, 95% CI 1.07–1.63) when compared to white persons. Black persons had a higher crude prevalence of OHT, but this became similar to that of white persons after adjusting for other factors.

Compared to patients with a primary diagnosis of anterior uveitis, patients with intermediate uveitis (aOR=0.80, 95% CI 0.68–0.94) and posterior uveitis (aOR=0.74, 95% CI 0.61–0.89) had a statistically significantly lower prevalence of OHT, whereas the lower prevalence in panuveitis cases (aOR=0.84, 95% CI 0.68–1.04) was not statistically significantly different from the prevalence in anterior uveitis cases. Eyes of patients with bilateral uveitis had a lower prevalence of OHT (aOR=0.31, 95% CI 0.26–0.37) than unilateral uveitis cases. Among systemic disease conditions affecting more than 4% of this population, only spondyloarthritis was associated with an altered (lower) risk of presenting OHT (aOR=0.61, 95% CI 0.50, 0.75).

Overall, eyes presenting with visual acuity (VA) worse than 20/40 were more likely to have OHT at presentation. Approximately 38% of uveitic eyes with VA worse than 20/40 but better than 20/200 had OHT 30 mmHg (aOR=1.33, 95% CI 1.12–1.56) while 18% with VA worse than 20/200 had OHT 30 mmHg (aOR=1.16, 95% CI 0.91–1.47) when compared to eyes with VA of 20/40 and better.

Eyes which had undergone cataract surgery prior to presentation had a more than a two-fold higher prevalence (aOR=2.24, 95% CI 1.84–2.72) of having OHT 30mmHg when compared with eyes that had no prior cataract surgery. A history of anti-glaucoma surgery or IOP reducing drops in the contralateral eye was exceptionally strongly associated with OHT of 30 mmHg in the ipsilateral eye (aOR=69.2, 95% CI 54.4–87.9) when compared to patients who had no such history. OHT prevalence varied by anterior chamber cell grade (overall $p<0.001$), with mild amounts of anterior chamber cells (0.5+) being associated with increased prevalence of OHT (aOR=1.36, 95% CI 1.14–1.61) and larger amounts of anterior chamber cells (2+ or more) tending to be associated with a lower prevalence of OHT (aOR=0.81, 95% CI 0.65–1.01). Eyes with anterior chamber inflammation sufficient to present with hypopyon had a lower prevalence of IOP elevation (aOR=0.26, 95% CI 0.07–0.94). Other markers of inflammatory activity were not significantly associated with presenting OHT. The presence of peripheral anterior synechiae (aOR=3.62, 95% CI 2.62–5.00) was more strongly associated with presenting OHT than the presence of posterior synechiae (aOR=1.18 (0.99, 1.42)). Among posterior segment findings studied, only the presence of epiretinal membrane was associated with higher prevalence of OHT at presentation (aOR=1.41, 95% CI 1.09–1.83).

Any daily use of topical corticosteroids increased the risk when compared to eyes that were not receiving any topical corticosteroids, with a slight dose-response relationship wherein >8drops/day having the highest prevalence of OHT (aOR=3.42, 95% CI 2.64–4.42). Oral corticosteroid and immunosuppressive therapy use were associated with a lesser—but still statistically significant—degree of increased prevalence of OHT than topical corticosteroids (aOR 1.8), whereas prednisone doses $\leq$ 7.5 mg/day were not associated with increased presenting OHT $\geq$ 21 mm Hg. The strongest corticosteroid therapy-prevalent OHT association was seen in eyes that were status post corticosteroid implant (aOR=29.1, 95% CI 4.81–176).

Incidence of Ocular Hypertension

A total of 4,843 uveitic eyes (31.4 %) that were without OHT developed IOP $\geq$ 21 mmHg during 9,766 eye-years of observation, an incidence rate of 14.4% per eye year (95% CI 13.4%, 15.5%). The annual incidence rate of OHT of $\geq$ 30 mmHg during the study period was 5.1%/eye-year (95% CI: 4.7%, 5.6%). Incident OHT (or starting medication to treat it) was common in the first two years, over which time 14% of eyes at risk had developed OHT of $\geq$ 30 mmHg, one-third had developed OHT $\geq$ 21 mmHg and one-fifth had developed an increase of IOP for 10 or more mmHg from baseline (see Figure 1).

Crude and adjusted significant associations of risk factors for developing the three independent categories of OHT are given in Table 3, whereas results for all potential risk factors studied are given in Table 4 (available at <http://aaojournal.org>). As with the risk factors for presenting IOP elevation, the patterns of association were similar across the alternative outcomes, so the summary below summarizes risk factors for incident OHT $\geq$ 30 mmHg for simplicity.

Similar to the prevalence analysis results, the risk of incident OHT $\geq$ 30 mmHg among those initially free thereof was lower among eyes of patients with bilateral uveitis compared with unilateral uveitis (adjusted Hazard Ratio (aHR) = 0.69, 95% CI: 0.54 – 0.88), and incident OHT was associated with worse visual acuity. Patients developing OHT of $\geq$ 30 mmHg more often had low vision (worse than 20/40 but better than 20/200) (aHR=1.44, 95% CI 1.18–1.75) and legal blindness (20/200 or worse) (aHR=1.47, CI 1.15–1.89) when compared to better visual acuity (20/40 or better). However, there were some differences from the prevalence analysis results. Eyes of patients with systemic hypertension (aHR = 1.29, 95% CI: 1.05–1.58) had a slightly higher incidence than non-hypertensive cases, whereas no association was observed in the prevalence analysis. In contrast to the results from the prevalence analysis, eyes of black individuals (aHR=1.54, 95% CI: 1.22, 1.96) and cases of panuveitis (with respect to anterior uveitis, aHR=1.48, 95% CI: 1.16, 1.90) tended to have higher incident OHT $\geq$ 30 mmHg, although the same pattern was not observed for OHT $\geq$ 21 mmHg and for a rise of 10 mmHg from the initial IOP. The pattern of (modest) association with prior surgery differed from that in the prevalence analysis, with a higher incidence of OHT $\geq$ 30 mmHg among eyes status post pars plana vitrectomy (aHR of 1.87, 95% CI 1.37 – 2.56) when compared to eyes that did not undergo a pars plana vitrectomy (no associated in the prevalence analysis) and little association with cataract surgery status (elevated risk at

presentation). As anticipated, eyes that had a history of hypotony had a lower incidence of OHT than those free of prior hypotony (aHR=0.43, 95% CI 0.23–0.83).

In a time-updated analysis, if there was a history of having developed OHT in one eye by the point of observation, the risk of developing IOP of ≥ 30 mmHg increased in the other eye. If one eye had an OHT of ≥ 21 but <30 mmHg, the risk of developing IOP of ≥ 30 mmHg in the contralateral eye was more than two and a half times (aHR=2.68, 95% CI 2.21–3.26) and if one eye had an OHT of ≥ 30 mmHg the risk of developing ≥ 30 mmHg in the contralateral eye increased nearly 5-fold (aHR=4.86, 95% CI 3.07–7.68). If there was history of using anti-glaucoma drops or surgery in one eye, the risk of developing ≥ 30 mmHg in the contralateral eye was more than 4 fold (aHR=4.17, 95% CI 3.21–5.43).

The time-updated presence of anterior chamber cells in the eyes was associated with increased risk of developing OHT ≥ 30 mmHg in a dose-response manner; grade 0.5+ (aHR=1.09, 95% CI 0.86–1.38), grade 1+ (aHR=1.43, 95% CI 1.07–1.91) and grade 2+ (aHR=1.59, 95% CI 1.20–2.10) when compared with eyes that were free of anterior chamber cells. Similarly, the presence of keratic precipitates at a given visit was associated with higher risk of incident OHT ≥ 30 mmHg (aHR=1.49, 95% CI: 1.09, 2.04). Similar to the prevalence analysis, higher risk of OHT ≥ 30 mmHg also was observed in eyes that had epiretinal membrane (aHR=1.25, 95% CI 1.01–1.55) and in eyes that had peripheral anterior synechiae (aHR=1.81, 95% CI 1.28–2.25).

In time-updated analyses, all forms of corticosteroid treatment increased the risk of developing OHT ≥ 30 mmHg, with the exception of systemic corticosteroid therapy (prednisone or equivalent) at a dosage ≤ 7.5 mg/day (aHR=1.10, 95% CI 0.78–1.55, compared to patients who did not receive systemic corticosteroids). Patients treated with systemic corticosteroids (prednisone or equivalent) at a dosage of >7.5 mg/day had a modest increase in the incidence of OHT ≥ 30 mmHg (aHR = 1.86, 95% CI 1.50–2.29). Periocular corticosteroids within the last three months increased the risk by more than 2 fold (aHR=2.34, 95% CI 1.67–3.26). Intravitreal corticosteroid implants had the highest risk, with an almost 10 fold increase (aHR=9.75, 95% CI 2.44–39.0). Eyes treated with topical corticosteroids showed a dose response increase. Even one drop per day was associated with a higher risk of OHT ≥ 21 mmHg or a rise by 10 mmHg and tended to be associated with higher risk of OHT ≥ 30 mmHg, and the risk generally increased with increasing dose for all ocular hypertensive outcomes for 2 drops/day or more (prednisolone acetate 1% or equivalent) (see Figure 2). However, the magnitude of increased risk of OHT observed with topical corticosteroids was less than we had observed in children,²⁰ with the risk peaking at 2.58-fold (95% CI: 1.85–3.60) with doses of ≥ 8 drops of prednisolone acetate 1% (or equivalent).

Elderly patients; races other than whites, blacks or Hispanics; panuveitis (vs. anterior uveitis); hyperlipidemia; spondyloarthritis; prior cataract surgery (time-updated); and posterior synechiae had a crude association with OHT of ≥ 30 mmHg that was abrogated by adjustment for confounding by other factors.

Incident OHT of ≥ 21 mmHg and incident rise in IOP by ≥ 10 mmHg had similar risk factor profiles as that of OHT of ≥ 30 mmHg except that a longer duration of uveitis was associated with a significantly lower risk of both incident OHT ≥ 21 mmHg and incident IOP increase ≥ 10 mmHg, whereas the association with incident IOP of ≥ 30 mmHg was not statistically significant.

DISCUSSION

Our study of a large number of adult eyes with non-infectious uveitis demonstrates that the risk of OHT in these cases is very high, with one third and one in seven respectively developing IOP ≥ 21 mmHg and IOP ≥ 30 mmHg (and/or requiring IOP-lowering therapy) within 2 years of follow-up. The incidence of IOP elevation events continued to increase substantially over time through at least ten years, suggesting that dichotomization of cases into cases prone to IOP elevation (e.g., “corticosteroid responders”) and those unlikely to develop IOP elevation may be unduly simplistic, and that all cases require continued observation for OHT throughout their clinical course.

The incidence we observed is a higher incidence rate than reported by previous smaller studies: Neri et al,²⁶ reported that in 337 patients with chronic uveitis, the incidence of “glaucoma” at 1, 5 and 10 years was 6.5% and 11.1% and 22.7% respectively; Shrestha et al reported the incidence of OHT in 116 consecutive new uveitis patients that were followed through 6 weeks to be 20%, mostly corticosteroids-induced (65%).²⁷ However, it is difficult to compare the results of these studies, because the criteria used to define the main outcome of interest was different for each study. Our study looked at ocular hypertension (OHT ≥ 21 mmHg, OHT ≥ 30 mmHg, and IOP increase of more than 10 mmHg from baseline), while the study by Neri et al, looked at incidence of “glaucoma” defined as elevated IOP ≥ 21 mmHg requiring continuous anti-glaucoma treatment, with or without glaucomatous optic disc abnormalities, a narrower definition. Nevertheless, all the studies agree that the incidence of IOP elevation to clinically important degrees is high in the setting of uveitis.

The large scale of our study permitted exploration of a broad range of potential demographic, ocular and systemic risk factors for OHT. Our results regarding OHT risk associations with systemic diseases in uveitis patients was mixed. Several epidemiological studies have shown the association of systemic hypertension with OHT in the general population,^{28–30} which we confirmed. In other studies with more detailed blood pressure measurements, the mean IOP appears to show a linear increase with increasing systolic and diastolic systemic blood pressures,³¹ and decreasing the high systolic or diastolic blood pressures by more than 10 mmHg over a 5 year period was associated with a corresponding decrease in IOP,³² suggesting that incident elevation of IOP in hypertensive patients with chronic uveitis could be mitigated to a small degree by exercising good control of systemic hypertension in at least some cases. Although several studies in non-uveitis populations have shown possible associations between diabetes mellitus and raised IOP, our analysis did not corroborate such an association in a uveitis population.^{33–35} Severe forms of OHT with IOP above 40 mmHg have been reported in uveitic patients with sarcoidosis.³⁶ In our study, sarcoidosis tended to be associated with a modestly increased crude prevalence and incidence of OHT, but these associations did not remain after adjusting for other factors,

suggesting that confounding known risk factors such as corticosteroid use, active inflammation, and intraocular scarring could be a substantial contributor to rises in IOP in sarcoidosis case. Spondyloarthritis was associated with a lower risk of both prevalent and incident OHT, which may reflect its remitting pattern of disease in which a number of visits of cases occurred while cases were in remission.

Eyes that had poor vision at presentation were twice as likely to develop OHT when compared to eyes that had good vision at first presentation. It is likely that poor vision is a marker for disease severity. Cataract surgery prior to the first visit at the tertiary uveitis clinic was associated with an increased risk for OHT at presentation but was not significantly associated with the incidence of OHT (IOP ≥ 30 mmHg) thereafter. An earlier study had reported an association between hypotony and cataract surgery in this cohort of patients.³⁷ Perhaps for similar reasons, eyes that had undergone pars plana vitrectomy for indications other than retinal detachment were also two and half times more likely to develop OHT, a finding that is similar to two other studies reporting on the increased risk of open angle glaucoma after vitrectomy.^{38–40} Lower vision, need for cataract surgery, and need for vitrectomy likely all serve as indicators for more severe disease and thus higher risk of IOP elevation; hypotony may reflect extreme disease severity with ciliary body damage explaining the association with hypotony as well as OHT in this cohort. As expected, the presence of peripheral anterior synechiae (PAS) almost doubled the risk of developing OHT ≥ 30 mmHg; a third of eyes which had evidence of PAS recorded by chart review developed OHT at 2 years. The association may be underestimated, as gonioscopy may not have been performed in every case in this retrospective study. This finding is in contrast to a previous, smaller study that followed up uveitis patients for six months and found that PAS causing OHT was not a significant finding in their cohort, which they attributed to regular use of mydriatics while treating uveitis.^{41,42} Perhaps with the more advanced disease seen in some cases at tertiary centers like ours, PAS was sufficiently extensive in enough patients as to lead to a statistically significant effect. It is difficult to be certain why bilateral disease would be protective against OHT, unless it reflects a greater tendency to use immunosuppressive therapy which may be protective by minimizing corticosteroid use.

Our study also shows that patients have a very high risk of developing OHT in one eye if the other eye had developed OHT earlier. Further, these high relative risks are seen together with high absolute risks, emphasizing the high degree of importance of monitoring the contralateral eye when a unilateral increase of IOP occurs in a patient undergoing treatment for uveitis.

The increased risk of developing OHT associated with corticosteroid use has been recognized for several decades and this large study where uveitis was treated with different types of corticosteroids for different durations further quantifies these relationships. The only group of cases receiving corticosteroids which did not have a higher risk were those receiving oral corticosteroids at a dose of 7.5 mg/day or less of prednisone. If the prednisone or equivalent corticosteroid intake was more than 7.5mg/day of prednisone, the risk of OHT almost doubled when compared with patients receiving no systemic corticosteroids. The discordance observed between prevalence and incidence on the risk of having a dosage of more than 7.5mg/day of prednisone or equivalent would indicate that the incidence result is

a more robust way of ascertainment. Avoiding the risk of elevated IOP with doses of corticosteroids as low as possible (or, if possible, preferably none at all) is in addition to the value of lower doses in avoiding systemic conditions as osteoporosis, osteonecrosis, myopathy, endocrine and other metabolic effects.⁴³

Use of topical corticosteroid therapy increases the risk of OHT in a dose-response manner over and above high absolute risk of OHT in this population, and the risk was increased for some of the outcomes studied even at a dose of 1 drop per day (prednisolone acetate 1% or equivalent). This observation further supports the practice of minimizing topical corticosteroid dosage, and suggests that even eyes on low maintenance doses of topical corticosteroids have a very substantial risk of serious IOP elevation, which must be managed carefully if this approach is to be used. However, the degree of increased risk with increasing topical corticosteroid dose was not as steep as we had observed in children, suggesting that children might more likely have IOP elevation on the basis of corticosteroid responsiveness. Eyes with uveitis treated with periocular corticosteroid injections within the last three months had more than doubled risk of developing OHT. Fluocinolone acetonide intravitreal implants had the largest ocular hypertensive effect among corticosteroid therapies, with a 10 fold higher risk, which is a well-documented pattern.^{5,44–47} All eyes under active treatment with corticosteroids should be continuously monitored for elevated IOP, as our data suggest that there is ongoing risk even if cases have not been observed to have elevated IOP in the first few visits.

Limitations of our study include the fact that in these chart review data, IOP values were not taken by the same type of instrument in all cases and were not corrected for age or corneal thickness, factors known to affect IOP measurements modestly, but unlikely to affect our qualitative conclusions substantially. Data also were collected from academic uveitis specialty practices that probably had more severe disease than patients attending general ophthalmology clinics would have had, so it is possible that risks would have been less in a general ophthalmology cohort otherwise managed in the same way. Data also were collected over a long period of time. However, sensitivity analyses evaluating the large majority measured using Goldmann tonometry and in the last ten years of the study showed no clear differences in the patterns observed. Also patients were observed from their first visit rather than from initial diagnosis with uveitis; however, duration of uveitis prior to cohort entry was not an important predictive factor regarding OHT. Current corticosteroid doses might have been lower than what had been in use in the interval before observation of IOP; thus the association with lower doses might be somewhat overestimated. Cumulative lifetime corticosteroid use could not be calculated. The risk of IOP ≥ 30 mmHg probably is overestimated to some extent as eyes sometimes are started on IOP-lowering therapy prior to reaching that threshold and may never have reached it, or may have reached it later. Whether IOP elevation was reversible or irreversible also could not be addressed in our analysis, because IOP-lowering therapy often is continued after being started. While we cannot differentiate directly between whether the corticosteroid use itself or the indication for such use as to which is the stronger risk factor, the dose response relationship observed with higher eye drop doses combined with the typical practice pattern of using high doses initially in most patients would suggest the drug itself probably has the greater effect. Strengths of the study include a large sample size, standardized data collection across

multiple centers, and detailed information on ocular and systemic aspects of the study participants.

In conclusion, our study suggests that the risk of IOP elevation to a clinically important degree is exceptionally high in uveitis cases, especially cases with contralateral IOP elevation, those using corticosteroids, and those with severe disease as indicated by poor presenting vision, need for surgeries, and peripheral anterior synechiae. Several other risk factors also increase the risk, and such increases over and above the high basal level of absolute risk are clinically important. All cases of uveitis should be assessed for OHT at every visit (including among those who initially do not seem to be “corticosteroid responders”). Efforts should be made to minimize use of corticosteroid therapy while maintaining control of inflammation using corticosteroid-sparing methods when indicated,⁴⁸ particularly over the long term, so as to lower the risk of OHT in addition to the other benefits of this approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Kaplan Meier estimates of the incidence of the three categories of ocular hypertension (Intraocular pressure (IOP) ≥ 21 mmHg, IOP ≥ 30 mmHg, and a rise in IOP from the first visit by ≥ 10 mmHg). Eyes starting medical or surgical treatment for IOP elevation in the interval also were counted as events. Each Kaplan Meier curve includes those eyes initially at risk (free of the event) as the beginning of follow-up; thus eyes could have been included in more than one of the Kaplan Meier curves. At risk patients for the ≥ 21 group started at 4843 and ended at 198 and the ≥ 10 group started at 5304 and ended at 267.

Figure 2.

Box plot displaying the risk associations of the three types of ocular hypertension (Intraocular pressure (IOP) ≥ 21 mmHg, IOP ≥ 30 mmHg, and a rise in IOP from the first visit by ≥ 10 mmHg) with different forms of corticosteroid therapy.

Table 1

Prevalence and Significant Risk Factors for ocular hypertension (> 21 mmHg, 30 mmHg) in Noninfectious Uveitis adults at Presentation.

Variable		IOP* : n (%)					IOP 21			IOP 30		
		<21	21 – <30	30	Crude		Adjusted*		P	Crude		Adjusted**
Age at presentation (years)	18–29	1688 (89.9%)	150 (8.0%)	40 (2.1%)	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	<0.001	Odds Ratio (95% CI)	p	P
	30–44	3578 (88.5%)	389 (9.6%)	75 (1.9%)	0.58 (0.49, 0.69)	<0.001	0.67 (0.56, 0.80)	<0.001	0.56 (0.45, 0.69)	0.63 (0.51, 0.77)	<0.001	<0.001
	45–64	3480 (85.0%)	494 (12.1%)	120 (2.9%)	0.65 (0.57, 0.74)		0.77 (0.68, 0.89)		0.59 (0.50, 0.69)	0.70 (0.60, 0.81)		
	65+	1181 (82.1%)	202 (14.0%)	55 (3.8%)	1		1		1	1		
					1.58 (1.35, 1.84)		1.20 (1.01, 1.42)		1.74 (1.46, 2.07)	1.25 (1.04, 1.51)		
Sex	Male	3529 (87.1%)	411 (10.1%)	112 (2.8%)	1	0.95	1	0.046	1	1	0.33	<0.001
	Female	6398 (86.5%)	824 (11.1%)	178 (2.4%)	0.997 (0.89, 1.11)		0.89 (0.79, 0.998)		0.94 (0.82, 1.07)	0.75 (0.66, 0.85)		
Race category	White	7362 (87.3%)	887 (10.5%)	185 (2.2%)	1	<0.001	1	0.35	1	1	<0.001	0.047
	Black	1249 (83.3%)	188 (12.5%)	63 (4.2%)	1.54 (1.33, 1.79)		1.05 (0.89, 1.25)		1.69 (1.42, 2.01)	1.07 (0.89, 1.29)		
	Hispanic	379 (85.7%)	55 (12.4%)	8 (1.8%)	1.23 (0.94, 1.62)		1.28 (0.97, 1.69)		1.19 (0.86, 1.65)	1.21 (0.92, 1.59)		
	Other	937 (87.1%)	105 (9.8%)	34 (3.2%)	1.06 (0.88, 1.27)		1.06 (0.88, 1.28)		1.19 (0.96, 1.47)	1.32 (1.07, 1.63)		
Uveitis Category	Anterior	4517 (85.4%)	617 (11.7%)	154 (2.9%)	1	<0.001	1	0.06	1	1	<0.001	0.004
	Intermediate	2332 (88.7%)	250 (9.5%)	46 (1.8%)	0.71 (0.62, 0.82)		0.82 (0.70, 0.95)		0.68 (0.58, 0.81)	0.80 (0.68, 0.94)		
	Posterior	2005 (88.8%)	218 (9.7%)	36 (1.6%)	0.68 (0.59, 0.80)		0.86 (0.73, 1.02)		0.58 (0.48, 0.70)	0.74 (0.61, 0.89)		
	Panuveitis	1073 (84.0%)	150 (11.7%)	54 (4.2%)	1.12 (0.95, 1.33)		0.93 (0.76, 1.13)		1.13 (0.93, 1.38)	0.84 (0.68, 1.04)		
Bilateral Uveitis	No	1817 (85.2%)	237 (11.1%)	78 (3.7%)	1	0.02	1	<0.001	1	1	0.004	<0.001
	Yes	8110 (87.0%)	998 (10.7%)	212 (2.3%)	0.87 (0.78, 0.98)		0.55 (0.48, 0.63)		0.82 (0.72, 0.94)	0.31 (0.26, 0.37)		
Visual Acuity	20/40 or better	5470 (87.7%)	639 (10.2%)	127 (2.0%)	1	<0.001	1	0.04	1	1	<0.001	0.003
	>20/40 – <20/200	3088 (85.5%)	413 (11.4%)	111 (3.1%)	1.40 (1.26, 1.56)		1.18 (1.04, 1.34)		1.55 (1.37, 1.75)	1.33 (1.12, 1.56)		
	20/200 or worse	1351 (85.4%)	179 (11.3%)	52 (3.3%)	1.55 (1.35, 1.78)		1.12 (0.93, 1.35)		1.73 (1.47, 2.03)	1.16 (0.91, 1.47)		
Spondyloarthritis	No	8418 (86.2%)	1083 (11.1%)	269 (2.8%)	1	<0.001	1	<0.001	1	1	<0.001	<0.001
	Yes	1509 (89.7%)	152 (9.0%)	21 (1.2%)	0.66 (0.56, 0.77)		0.69 (0.58, 0.82)		0.58 (0.47, 0.71)	0.61 (0.50, 0.75)		
Prior cataract surgery	Never	8695 (87.5%)	1020 (10.3%)	222 (2.2%)	1	<0.001	1	<0.001	1	1	<0.001	<0.001
	Prior to SITE	1228 (81.3%)	215 (14.2%)	68 (4.5%)	2.96 (2.59, 3.37)		1.57 (1.33, 1.85)		4.01 (3.48, 4.63)	2.24 (1.84, 2.72)		
	No Drops/Surgery	8955 (88.6%)	965 (9.6%)	184 (1.8%)	1	<0.001	1	<0.001	1	1	<0.001	<0.001
Other Eye History	Drops/Surgery	972 (72.1%)	270 (20.0%)	106 (7.9%)	25.8 (21.7, 30.8)		24.3 (20.1, 29.4)		54.3 (44.8, 65.8)	69.2 (54.4, 87.9)		
	Quiet	5418 (87.1%)	680 (10.9%)	125 (2.0%)	1	<0.001	1	<0.001	1	1	<0.001	<0.001

Variable			IOP* : n (%)					IOP 21				IOP 30			
			<21	21 – <30	30	Crude		Adjusted*		Crude		Adjusted**			
						Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p		
	0.5+		1873 (84.6%)	268 (12.1%)	73 (3.3%)	1.51 (1.33, 1.70)		1.11 (0.97, 1.28)		1.79 (1.55, 2.06)		1.36 (1.14, 1.61)			
	1+		1230 (85.5%)	161 (11.2%)	48 (3.3%)	1.28 (1.11, 1.49)		1.0004 (0.84, 1.19)		1.41 (1.18, 1.68)		1.11 (0.89, 1.37)			
	2+ or worse		1381 (89.3%)	122 (7.9%)	43 (2.8%)	0.89 (0.76, 1.04)		0.70 (0.59, 0.85)		0.999 (0.83, 1.20)		0.81 (0.65, 1.01)			
Hypopyon	No		9870 (86.6%)	1232 (10.8%)	289 (2.5%)	1	0.11	1	0.04	1	0.14	1	0.04		
	Yes		48 (92.3%)	3 (5.8%)	1 (1.9%)	0.52 (0.23, 1.17)		0.38 (0.15, 0.97)		0.46 (0.16, 1.28)		0.26 (0.07, 0.94)			
Peripheral Syneciae	No		9671 (87.3%)	1157 (10.4%)	247 (2.2%)	1	<0.001	1	<0.001	1	<0.001	1	<0.001		
	Yes		244 (67.4%)	75 (20.7%)	43 (11.9%)	5.15 (4.04, 6.58)		3.18 (2.39, 4.22)		5.90 (4.59, 7.59)		3.62 (2.62, 5.00)			
Immunosuppressive therapy/Biologic	No		8960 (86.9%)	1095 (10.6%)	259 (2.5%)	1	<0.001	1	0.06	1	<0.001	1	0.02		
	Yes		967 (85.0%)	140 (12.3%)	31 (2.7%)	1.41 (1.19, 1.66)		1.20 (0.99, 1.44)		1.50 (1.24, 1.82)		1.28 (1.03, 1.58)			
Prior Fluocinolone Acetonide Implant	No		9924 (86.7%)	1234 (10.8%)	289 (2.5%)	1	0.03	1	0.02	1	0.008	1	<0.001		
	Yes		3 (60.0%)	1 (20.0%)	1 (20.0%)	13.5 (1.35, 134)		12.0 (1.60, 89.3)		22.1 (2.22, 220)		29.1 (4.81, 176)			
Systemic Corticosteroids	None		7944 (87.3%)	934 (10.3%)	224 (2.5%)	1	<0.001	1	0.02	1	<0.001	1	0.007		
	<=7.5/day		96 (86.5%)	10 (9.0%)	5 (4.5%)	1.59 (0.95, 2.66)		1.09 (0.65, 1.83)		2.00 (1.16, 3.46)		1.81 (1.04, 3.14)			
	>7.5/day		1887 (84.3%)	291 (13.0%)	61 (2.7%)	1.35 (1.19, 1.54)		1.23 (1.07, 1.42)		1.36 (1.17, 1.58)		1.22 (1.04, 1.42)			
Topical Corticosteroids (per day)	None		5527 (90.1%)	500 (8.1%)	108 (1.8%)	1	<0.001	1	<0.001	1	<0.001	1	<0.001		
	1 drop		601 (86.0%)	86 (12.3%)	12 (1.7%)	2.17 (1.76, 2.68)		1.83 (1.44, 2.31)		2.48 (1.94, 3.16)		2.24 (1.71, 2.94)			
	2 drops		674 (80.3%)	140 (16.7%)	25 (3.0%)	2.89 (2.40, 3.48)		2.36 (1.93, 2.89)		3.46 (2.79, 4.28)		3.02 (2.37, 3.85)			
	3 drops		457 (78.4%)	103 (17.7%)	23 (3.9%)	2.90 (2.34, 3.60)		2.70 (2.13, 3.43)		3.27 (2.56, 4.18)		3.33 (2.54, 4.38)			
	4 drops		1079 (81.7%)	191 (14.5%)	51 (3.9%)	2.47 (2.11, 2.89)		1.90 (1.59, 2.26)		3.07 (2.55, 3.70)		2.38 (1.94, 2.94)			
	5–8 drops		808 (84.5%)	115 (12.0%)	33 (3.5%)	2.24 (1.87, 2.68)		2.23 (1.82, 2.74)		2.71 (2.20, 3.33)		3.09 (2.41, 3.96)			
	>8 drops		781 (85.0%)	100 (10.9%)	38 (4.1%)	2.09 (1.74, 2.51)		2.42 (1.95, 3.01)		2.51 (2.03, 3.12)		3.42 (2.64, 4.42)			
Epiretinal Membrane	No		9296 (86.8%)	1144 (10.7%)	270 (2.5%)	1	<0.001	1	0.052	1	<0.001	1	0.008		
	Yes		626 (85.1%)	90 (12.2%)	20 (2.7%)	1.44 (1.20, 1.74)		1.24 (0.998, 1.54)		1.54 (1.25, 1.91)		1.41 (1.09, 1.83)			

* IOP: Intraocular Pressure

** Adjusted by race, bilateral uveitis, visual acuity, hypertension, cataract surgery, pars plana vitrectomy (not for retinal detachment), other eye history, anterior chamber cells, epiretinal membrane, band keratopathy, peripheral synechiae, steroid implants, systemic steroid, and topical steroids.

95% CI = 95% Confidence Interval.

Activity measurements (inflammatory activity, vitreous cells and haze, and keratic precipitates) are not adjusted by Anterior Chamber cells.

Table 3

Incidence and Significant Risk Factors for ocular hypertension (> 21 mmHg– 30 mmHg) in Noninfectious Uveitis over 2-Year Period.

Variable		IOP < 21					IOP ≥ 30				
		Crude					Crude				
		Events/At Risk *	2-year IncidenceEstimate (95% CI)	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	Events/At Risk *	2-year IncidenceEstimate (95% CI)	Hazard Ratio (95% CI)	p
Sex	Male	489/1658 (29.5%)	0.34 (0.31, 0.37)	1	0.60	1	0.54	230/1784 (12.9%)	0.14 (0.11, 0.16)	1	0.49
	Female	1033/3185 (32.4%)	0.35 (0.32, 0.37)	1.03 (0.91, 1.18)		0.96 (0.84, 1.10)		493/3486 (14.1%)	0.14 (0.13, 0.16)	1.07 (0.88, 1.29)	
Bilateral Uveitis	No	223/803 (27.8%)	0.37 (0.33, 0.41)	1	0.17	1	0.03	114/882 (12.9%)	0.17 (0.14, 0.20)	1	0.055
	Yes	1299/4040 (32.2%)	0.34 (0.32, 0.36)	0.90 (0.77, 1.05)		0.83 (0.69, 0.98)		609/4388 (13.9%)	0.14 (0.12, 0.15)	0.81 (0.66, 1.004)	
Visual Acuity *	20/40 or better	660.4/2844.1 (23.2%)	0.30 (0.28, 0.32)	1	<0.001	1	0.048	228.9/3108.4 (7.4%)	0.10 (0.09, 0.11)	1	<0.001
	>20/40 – <20/200	455.3/1563.5 (33.4%)	0.41 (0.38, 0.44)	1.49 (1.32, 1.69)		1.17 (1.02, 1.34)		218.5/1456.1 (15.0%)	0.19 (0.16, 0.21)	2.00 (1.66, 2.40)	
	20/200 or worse	190.9/635.4 (30.0%)	0.37 (0.32, 0.41)	1.29 (1.09, 1.53)		1.01 (0.84, 1.21)		119.8/705.5 (17.0%)	0.21 (0.18, 0.25)	2.29 (1.84, 2.86)	
	<6 Months	649/1975 (32.9%)	0.38 (0.35, 0.41)	1	<0.001	1	<0.001	272/2137 (12.7%)	0.14 (0.12, 0.16)	1	0.04
Duration of uveitis prior to presentation	6 Months to <2 Years	329/938 (35.1%)	0.38 (0.34, 0.41)	0.97 (0.83, 1.14)		0.88 (0.75, 1.02)		177/1041 (17.0%)	0.17 (0.14, 0.20)	1.25 (0.995, 1.57)	
	2 to <5 Years	237/789 (30.0%)	0.31 (0.27, 0.35)	0.77 (0.64, 0.92)		0.76 (0.63, 0.91)		121/867 (14.0%)	0.14 (0.11, 0.16)	0.98 (0.75, 1.27)	
	5+ Years	307/1141 (26.9%)	0.28 (0.24, 0.31)	0.67 (0.57, 0.79)		0.69 (0.58, 0.81)		153/1225 (12.5%)	0.12 (0.10, 0.14)	0.86 (0.68, 1.09)	
	Never	1277/4236.6 (30.1%)	0.34 (0.32, 0.36)	1	0.02	1	0.002	517/4525.1 (11.4%)	0.13 (0.11, 0.14)	1	<0.001
Prior cataract surgery *	Prior to Cohort Entry	150/449 (33.4%)	0.33 (0.28, 0.38)	0.98 (0.81, 1.18)		0.67 (0.54, 0.84)		99/500 (19.8%)	0.19 (0.15, 0.23)	1.59 (1.25, 2.03)	
	During Follow-up	44.6/153.4 (29.1%)	0.45 (0.36, 0.53)	1.44 (1.10, 1.86)		0.92 (0.70, 1.21)		44.2/240.9 (18.3%)	0.31 (0.24, 0.37)	2.73 (2.09, 3.57)	
Pars Plaua Vitrectomy (not for the Indication of Retinal Detachment) *	No	1431/4655.6 (30.7%)	0.34 (0.32, 0.36)	1	0.005	1	0.046	638/5024.8 (12.7%)	0.13 (0.12, 0.15)	1	<0.001
	Yes	62.1/187.4 (33.2%)	0.45 (0.36, 0.53)	1.46 (1.12, 1.91)		1.33 (1.005, 1.77)		58.2/245.2 (23.8%)	0.32 (0.24, 0.38)	2.68 (2.03, 3.53)	
Other Eye History of OHT *	Normal	1139/4224.5 (27.0%)	0.30 (0.28, 0.32)	1	<0.001	1	<0.001	353/4054.2 (8.7%)	0.10 (0.08, 0.11)	1	<0.001
	21 – <30	181.2/416 (43.6%)	0.63 (0.58, 0.68)	2.81 (2.43, 3.25)		2.49 (2.13, 2.90)		174.8/937 (18.7%)	0.25 (0.22, 0.29)	2.87 (2.37, 3.47)	
	>=30	13.3/33.2 (40.2%)	0.49 (0.29, 0.63)	1.89 (1.15, 3.09)		2.07 (1.26, 3.40)		15.5/59.9 (25.8%)	0.44 (0.29, 0.56)	5.76 (3.79, 8.76)	
	Drops/Surgery	69.1/169.3 (40.8%)	0.51 (0.44, 0.58)	2.02 (1.63, 2.51)		2.06 (1.65, 2.57)		63.1/218.9 (28.8%)	0.38 (0.31, 0.44)	4.64 (3.66, 5.88)	
Overall Inflammatory Activity *	Inactive	683.7/2853.2 (24.0%)	0.34 (0.31, 0.36)	1	0.19	1	0.11	313.9/3237.9 (9.7%)	0.13 (0.11, 0.15)	1	0.07
	Slightly active	136.7/575.3 (23.8%)	0.38 (0.33, 0.43)	1.18 (0.99, 1.40)		1.01 (0.83, 1.21)		56.7/598 (9.5%)	0.17 (0.13, 0.20)	1.31 (1.01, 1.70)	
	Active	381.9/1413.5 (27.0%)	0.34 (0.31, 0.37)	1.01 (0.88, 1.15)		0.83 (0.70, 0.999)		162.3/1433.1 (11.3%)	0.15 (0.13, 0.17)	1.17 (0.97, 1.42)	
	Quiet	830.2/3321.7 (25.0%)	0.32 (0.30, 0.34)	1	0.002	1	0.71	336.8/3676.1 (9.2%)	0.12 (0.10, 0.13)	1	<0.001
Anterior Chamber Cell Grade *	0.5+	187.8/770.9 (24.4%)	0.40 (0.35, 0.44)	1.31 (1.12, 1.53)		1.03 (0.88, 1.21)		74.5/814.1 (9.2%)	0.17 (0.13, 0.20)	1.45 (1.16, 1.83)	
	1+	97.2/400 (24.3%)	0.39 (0.33, 0.44)	1.27 (1.04, 1.55)		0.96 (0.76, 1.21)		43.4/410.1 (10.6%)	0.20 (0.16, 0.25)	1.83 (1.39, 2.41)	
	2+ or worse	74.8/350.4 (21.3%)	0.36 (0.30, 0.42)	1.16 (0.93, 1.44)		0.89 (0.70, 1.13)		42.2/369.7 (11.4%)	0.23 (0.18, 0.28)	2.09 (1.63, 2.70)	

Variable		IOP 21					IOP 30				
		Crude			Adjusted **		Crude			Adjusted **	
		Events/At Risk *	2-year IncidenceEstimate (95% CI)	Hazard Ratio (95% CI)	p		Events/At Risk *	2-year IncidenceEstimate (95% CI)	Hazard Ratio (95% CI)	p	
Peripheral Synchia *	No	1455/4725.4 (30.8%)	0.34 (0.32, 0.36)	1	0.001		653/5120.6 (12.8%)	0.13 (0.12, 0.15)	1	<0.001	
	Yes	55.8/116.6 (47.9%)	0.49 (0.38, 0.58)	1.61 (1.21, 2.16)			50.9/148.4 (34.3%)	0.36 (0.27, 0.44)	3.11 (2.30, 4.21)		
Current Systemic Corticosteroid Use *	None	935.4/3716.3 (25.2%)	0.29 (0.27, 0.31)	1	<0.001		424.3/4089 (10.4%)	0.12 (0.10, 0.13)	1	<0.001	
	7.5 mg/day	43.8/222.4 (19.7%)	0.32 (0.25, 0.38)	1.11 (0.85, 1.45)			26.8/286.2 (9.4%)	0.15 (0.11, 0.19)	1.29 (0.93, 1.79)		
	>7.5 mg/day	365.8/904.3 (40.5%)	0.53 (0.48, 0.57)	2.15 (1.87, 2.47)			153.2/894.9 (17.1%)	0.23 (0.20, 0.27)	2.14 (1.74, 2.62)		
Periocular Corticosteroids Use in the Last Three Months *	No	1389.8/4649.4 (29.9%)	0.33 (0.31, 0.35)	1	<0.001		660.2/5091.1 (13.0%)	0.14 (0.12, 0.15)	1	<0.001	
	Yes	62.8/193.6 (32.4%)	0.65 (0.57, 0.72)	2.64 (2.13, 3.28)			18.2/178.9 (10.2%)	0.32 (0.23, 0.40)	2.69 (1.94, 3.71)		
Topical Corticosteroids *	None	701.3/3053.3 (23.0%)	0.27 (0.25, 0.29)	1	<0.001		277.7/3377.6 (8.2%)	0.10 (0.08, 0.11)	1	<0.001	
	1 drop	54.1/288.2 (18.8%)	0.32 (0.25, 0.39)	1.23 (0.95, 1.59)			29/344.9 (8.4%)	0.15 (0.11, 0.20)	1.62 (1.16, 2.27)		
	2 drops	69.4/293.9 (23.6%)	0.46 (0.39, 0.53)	1.96 (1.56, 2.46)			34.5/335.3 (10.3%)	0.21 (0.15, 0.26)	2.24 (1.63, 3.08)		
	3 drops	52/205.5 (25.3%)	0.43 (0.34, 0.51)	1.76 (1.35, 2.31)			21.2/221.1 (9.6%)	0.19 (0.12, 0.25)	2.04 (1.38, 3.01)		
	4 drops	132.2/434.8 (30.4%)	0.49 (0.42, 0.54)	2.10 (1.73, 2.55)			57.8/440.2 (13.1%)	0.24 (0.18, 0.29)	2.63 (2.00, 3.46)		
	5–8 drops	74.2/266.8 (27.8%)	0.56 (0.47, 0.63)	2.55 (2.04, 3.20)			31.9/272.6 (11.7%)	0.27 (0.20, 0.33)	3.00 (2.18, 4.12)		
	>8 drops	95.6/300.4 (31.8%)	0.57 (0.48, 0.64)	2.64 (2.08, 3.34)			43.3/278.4 (15.6%)	0.31 (0.23, 0.38)	3.65 (2.68, 4.97)		
Fluocinolone Acetonide Implant *	No	1517/4840.1 (31.3%)	0.34 (0.32, 0.36)	1	0.005		718/5266.5 (13.6%)	0.14 (0.13, 0.15)	1	<0.001	
	Yes	1.7/2.9 (58.9%)	0.95 (0. 0.999)	6.94 (1.79, 27.0)			2/3.5 (56.2%)	0.88 (0. 0.99)	14.2 (4.42, 45.5)		
Epiretinal Membrane *	No	1241/4171.9 (29.7%)	0.33 (0.31, 0.35)	1	0.01		533/4419.9 (12.1%)	0.13 (0.12, 0.15)	1	<0.001	
	Yes	222.3/670.1 (33.2%)	0.39 (0.35, 0.44)	1.23 (1.05, 1.43)			146.3/849.1 (17.2%)	0.19 (0.15, 0.22)	1.47 (1.21, 1.80)		

* Time-varying characteristics potentially contribute partial time to more than one level of a covariate

** Adjusted by race, bilateral uveitis, visual acuity, hypertension, cataract surgery, pars plana vitrectomy (not for retinal detachment), other eye history, anterior chamber cells, epiretinal membrane, band keratopathy, peripheral synechia, steroid implants, systemic steroid, and topical steroids, 95% CI = 95% Confidence Interval. # IOP: Intraocular Pressure