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Evaluating the Impact of Uveitis on Visual Field Progression Using Large Scale Real-World Data

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Abstract

Purpose

To compare rates of visual field (VF) loss in uveitis patients with glaucoma against patients with primary open angle glaucoma (POAG) and explores the association between intraocular pressures (IOP) and rate of VF loss.

Design

Retrospective cohort study.

Methods

Anonymized VFs and IOP measurements extracted from the EMR of 5 regionally different glaucoma clinics in England. A total of 205 eyes with diagnosis of “uveitis” plus “glaucoma” were compared with 4600 eyes with “POAG” only. Minimum inclusion criteria was ≥4 visits within a 4-year window. Relative risk (RR) of being a “rapid progressor” (mean deviation (MD) loss ≥1.5 dB/year) was calculated. A mixed-effects model (MEM) and a pointwise VF progression analysis of pattern deviation was used to confirm differences between the groups. Longitudinal IOP mean, range and variability were compared with rate of VF progression.

Results

Median (IQR) baseline MD in the uveitis and POAG groups was –3.8 (-8.7, -1.5) dB and –3.1 (-6.6, -1.2) dB respectively. The uveitis and POAG groups had 23/205 (11%) and 331/4600 (7%) “rapidly progressing” eyes respectively. Age-adjusted RR for “rapid progression” in uveitic versus POAG eyes was 1.9 (95% CI:1.8-2.0). The MEM confirmed that uveitic eyes (-0.49 dB/year) showed higher rates of VF

progression than the POAG group (-0.37 dB/year; p<0.01). IOP range and variability were higher in the “rapidly progressing” uveitic eyes.

Conclusions

Our analysis suggests that VF loss occurs faster in glaucoma patients with uveitis than those without uveitis. The risk of progressing rapidly in glaucoma with uveitis is almost double than in those without uveitis. Early identification of “rapid progressors” may enable targeted intervention to preserve visual function in this high-risk group.

Evaluating the Impact of Uveitis on Visual Field Progression Using Large Scale Real-World Data

Short Title: Evaluating the Impact of Uveitis on Visual Field Loss

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Introduction

Uveitis remains the fourth most common cause of blindness in the working-age population throughout the developed world, with visual impairment affecting between 2.8 and 10% of uveitic patients.[1–4] Reduced visual function may result from direct damage to uveal tract structures, but more commonly occurs due to secondary tissue damage, with the most prevalent complications being cataract, macular oedema and glaucoma.[5] Of these, both cataract and macular oedema can be considered at least partially reversible, however visual impairment due to glaucoma is irreversible and thus early diagnosis and appropriate management of uveitic glaucoma is of paramount importance.

Glaucoma in the presence of uveitis can develop via a number of mechanisms.[6] Increases in intraocular pressure (IOP) can occur due to mechanical obstruction of aqueous outflow, presenting with secondary angle closure due to pupillary block from posterior synechiae, or more chronically following development of peripheral anterior synechiae or angle rubeosis. Secondary open angle glaucoma may develop due to chronic inflammatory damage to the trabecular meshwork, or in response to corticosteroid therapy. In addition, specific uveitis entities are associated with elevation of IOP, such Posner-Schlossmann syndrome, Fuch's heterochromic iridocyclitis and herpetic uveitis. Active inflammation, corticosteroid usage, increasing age, and number of years since diagnosis have each been demonstrated to be associated with raised IOP in uveitic patients.[7]

The prevalence of raised IOP in uveitis remains poorly defined, since increases in IOP may be transient and may not progress to true glaucomatous optic neuropathy. The prevalence of treated glaucoma varies from 20-30% in most cohorts.[5,7–9] Accurate stratification of patients at risk of uveitic glaucoma is necessary to identify those at high risk of irreversible vision loss. Intensive monitoring and active intervention are important to prevent irreversible visual impairment in these patients.[10]

With the widespread adoption of electronic medical records (EMR), it is now possible to collect clinical data from large patient populations, identifying trends in disease progression and treatment response which have not been possible with traditional paper-based records. Such 'Big Data' approaches have been successfully used to characterise the population and predict outcomes in other ophthalmic diseases.[11–15] This study aims to utilise large-scale EMR data for comparing the rate of visual field (VF) loss in uveitis patients with glaucoma, compared to those with primary open angle glaucoma (POAG), and explore whether this is associated with IOP.

Methods

Anonymised recorded data between April 2000 to March 2015 were extracted from the Medisoft (Medisoft Ltd., Leeds, UK) EMR from five regionally different glaucoma clinics in England and linked to the Royal College of Ophthalmologists' National Ophthalmology Database.[16] The data used were collected for a Healthcare Quality Improvement Partnership (HQIP) project conducted by the Royal College of Ophthalmologists (National Ophthalmology Database Audit provider) as part of the National Clinical Audit and Patient Outcomes Programme. The study adhered to the Declaration of Helsinki and all analyses of the data were approved by a research ethics committee of City, University of London. All patient data were anonymized and securely held on the university database. The resulting database contained records from 71,404 patients.

Inclusion criteria

Eyes were sorted into two groups based on EMR diagnostic labelling: a POAG group and a group of patients with both a 'uveitis' and 'glaucoma' diagnosis. POAG was defined by having a diagnostic label of 'POAG' or 'chronic open angle glaucoma (COAG)' without any uveitis co-pathologies. Uveitis plus glaucoma was defined as having both a label of POAG or COAG plus a uveitis label. A variety of anatomical and disease-specific labels for uveitis were included (full list of diagnostic labels in the **Appendix**). Initial extraction by diagnosis found 1,179 eyes with uveitic glaucoma and 21 209 eyes with POAG (**Figure 1**)**.** The inclusion criteria for each eye was a minimum of 4 VF tests over 4 years, with at least 4 of the included tests being performed within the initial 4 years **(Figure 2).** Only VFs from the Humphrey Field Analyser (HFA) using Goldmann size III (white-on-white) stimuli with the 24-2 test pattern acquired with either SITA Standard or SITA Fast testing algorithms were included.

A secondary analysis on the association between IOP behaviour and VF progression was also carried out. In addition to the above inclusion criteria, a minimum of 4 IOP measurements in the first 4 years were needed.

Statistical analysis

Analysis was carried out on one eye per patient; if a patient had two eligible eyes, one was chosen at random. The first VF examination of each series was defined as the baseline measurement. HFA pointwise sensitivity values and mean deviation (MD; an estimate of average VF sensitivity relative to healthy age matched controls) values were extracted for each VF for each eye. Pattern deviation (PD) pointwise values were calculated using the visualFields package in R.[18]

Ordinary least-squares (OLS) linear regression of MD over time was used to estimate rates of progression (dB/year). As with previous studies, a fast progressing VF series was defined as having a rate of progression slope of ≥1.5 dB/year.[13,19] A crude relative risk (RR) was calculated as the ratio of the proportion of fast progressors in the uveitis and POAG groups, for each 10-year age group from 40 to 100 years, as estimated by the OLS regression slopes. An overall age-adjusted RR was calculated using the direct method.[20]

Two secondary VF progression analyses were also performed. First, a linear mixed-effects model analysis**,** which can estimate the regression coefficient while including

both fixed and random effects was fitted.[21] MD was treated as a response variable, time (years since first visit), group (POAG or uveitis) and baseline age were treated as fixed effects and individuals as a random effect (model available in **Supplementary materials**).

Second, the permutation of pointwise linear regression (PoPLR) technique was used to analyse the pointwise sensitivities and PD values of each VF series.[22–24] PoPLR repeatedly permutes the order of VF visits in a series to give robust estimations of the likelihood of significant VF change. In our case PoPLR was performed on PD values as an indicator of worsening VF to mitigate global changes which may occur, for example, from developing cataract. The outcome of interest is simply the proportion of eyes showing statistically significant progression (at $p = 0.05$) in the uveitic and POAG groups.

IOP data were analysed using longitudinal metrics: mean, range and mean absolute error (MAE). Mean IOP was defined as the mean of all recorded IOP values in the series. IOP range was defined as the highest value (peak) minus the lowest value (trough) in the IOP series. MAE, as a measure of IOP variability, was estimated by fitting an OLS linear regression to IOP values over time, then extracting errors (predicted values minus the observed IOP) at each visit. The mean of the absolute values of these errors was the MAE value. Univariate associations between rates of progression and IOP metrics were analysed. Statistical comparisons were made using the Mann-Whitney U test.

Analysis was varied out using R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

From a starting population of 1,179 eyes, 205 (17%) eyes with uveitis plus glaucoma satisfied the inclusion criteria and were included in further analysis. From a starting population of 21,209 eyes, 4,600 (22%) eyes with POAG were included in further analysis (**Figure 2**). Median (interquartile range [IQR]) age of the patients was 64 (53, 73) and 70 (62, 76) years in the uveitis and POAG groups respectively. Baseline MD model estimates in the uveitis and POAG groups were –5.55 (95% CI: -6.39, -4.47) dB and –4.47 (95% CI: -4.31, -4.63) dB respectively. Median (IQR) Intensity (frequency) of VF testing was the same, with an interval of 10 months between each VF test, for both groups.

Rate of Visual Field loss

The uveitis and POAG groups had 23/205 (11%) and 331/4 600 (7%) eyes which progressed at ≥1.5 dB/year respectively. The crude RR of a fast rate of progression for uveitis/POAG was 1.6 (95% confidence interval [CI] 1.1 – 2.3) and age-adjusted RR was 1.9 (95% CI: 1.8 - 2.0). This indicates that, for a similarly aged population, a patient in the uveitis group was 1.9 times more likely to be a fast progressor than patients in the POAG group.

Further analysis using the mixed effects model showed that, the age-adjusted rate of progression was -0.49 dB/year for the uveitis group and -0.37 dB/year for the POAG group. The estimated average age-corrected difference in rate of progression between the groups at the mean age was -0.12 dB/year ($p < 0.01$)

VF progression analysis using PoPLR on PD values indicates that the uveitis group has a higher proportion of significantly progressing eyes (21.2%), compared to the POAG group (18.5%).

Longitudinal intraocular pressure (IOP) analysis

A total of 143 eyes with uveitis plus glaucoma and 3,386 eyes with POAG met the additional inclusion criteria for longitudinal IOP analysis. A summary of longitudinal IOP measurements can be found in **Table 1.** We did not find a statistically significant difference in mean IOP (within 1 mmHg) between the two groups, yet there was wider range and higher MAE in the uveitis group ($p<0.001$). A comparison between fast and non-fast progressors found the mean IOP difference to be within 1 mmHg for all groups. IOP range was wider in the fast progressors of both POAG and uveitis groups (both $p<0.05$), and widest in the fast progressing uveitis group (21 mmHg). Similarly, MAE was higher in fast progressors of both diseases ($p<0.01$), but highest in the fast progressing uveitis group (3.5 mmHg).

Discussion

This is the first study to utilize real world EMR data to compare rates of VF loss in uveitis patients with glaucoma and those with POAG. We have demonstrated that uveitis patients with a diagnosis of glaucoma were likely to be younger and have a worse MD at baseline than those with a diagnosis of POAG. The uveitis group were more likely to lose VF at a rapid rate (≥1.5 dB/year loss in MD) compared with the POAG group, with an age-adjusted RR of 1.9 (95% CI: 1.8 - 2.0). Despite this, our data show that the average frequency of VF monitoring is the same for both diseases. Our longitudinal IOP analysis suggests IOP range and variability had a stronger association with rapid VF loss than mean IOP.

Our findings suggest that patients with a combination of uveitis and glaucoma lose vision more rapidly than POAG, yet on average they are monitored with VFs at the same intensity. Our estimates of rate of VF loss in POAG (-0.37 dB/year) is higher than previously been reported in the literature, however our estimates differ in that were adjusted for age.[13,25] The observed proportion of fast progressors in our POAG cohort is also similar to previous studies: defined thresholds for 'fast' or 'rapid' progression in published literature range from ≥1 to 2 dB/year loss in MD, and reported prevalence of patients progressing rapidly varies between 3-17% in previous studies.[25–30]

The main strength of our study is the large starting sample size compared to others in the literature. Although only 205 uveitic eyes were included in our final VF progression analysis, a sufficiently large starting sample was required to reach the final 205 included samples. We restricted the inclusion of patients to those with a minimum of 4 VF tests over at least 4 years. Additionally, at least 4 of the included VF tests must have been performed within 4 years of the first test. As with our previous work, the minimum inclusion criteria was a compromise between maximising sample size whilst still ensuring robustness of our rate of progression estimates.[13,15]

Our study also has several limitations. Firstly, our data were reliant upon accurate recording in the EMR. Diagnostic labelling within the Medisoft EMR is not a mandatory field and can be entered as free-text, or not entered at all. We included a large list of diagnostic labels commonly found in the presence of uveitis to widen our capture of uveitis subjects. However, a large portion of uveitis subjects in this analysis were lacking in anatomical or disease-specific diagnostic labels in the EMR, thus limiting our ability to explore patterns in specific uveitis subtypes. We took steps in our analyses to mitigate the confounding effects of ocular comorbidities. For example, PoPLR VF progression analysis with PD values is designed to identify localised VF change and not just general reduction in VF sensitivity that might be attributed to developing cataract. Results from the PoPLR analysis supported our main findings. Nevertheless, we cannot fully account for the effects of ocular comorbidities on perimetric performance of the patients. Uveitic patients are susceptible to a range of complications such as cataract, cystoid macular edema, fibrin deposition, band keratopathy and epiretinal membrane, all of which may affect VF performance. Acute inflammatory processes may cause temporary drops in visual acuity, which subsequently resolves. This may explain why some patients' MD seems to improve over time (i.e. perhaps due to cataract surgery or resolution of inflammatory disease such as cystoid macular oedema), although this could also be attributed to patient variability and learning effect.[32–34] On the other hand,

progressive loss of visual acuity from longstanding uveitic damage (such as scarring and retinal atrophy) may also confound the apparent loss of MD in the uveitic group. Structural information such as retinal nerve fibre layer thickness, cup-to-disc ratio or the inclusion of imaging data would be useful for differentiating between true glaucomatous VF loss and global loss due to other causes. Although not available in this dataset, linkage of structural information would be of interest for future studies.

An important finding is the worse presenting MD in the uveitic group, suggesting early VF loss may be under-detected. Additionally, the baseline age in the uveitis plus glaucoma group was younger, which also supports the hypothesis that uveitic glaucoma may progress faster. Detecting early VF loss is clinically difficult if perimetric testing is not performed routinely, particularly in the absence of a deranged IOP. In the context of uveitis, controlling the inflammation may require more clinical urgency and early glaucomatous damage can be easily overlooked. On the other hand anti-inflammatory treatment, of which corticosteroids is the preferred first-line agent, can precipitate raised IOP in up to a third of patients.[35,36] Steroid implants have been shown to increase the risk of developing glaucomatous optic neuropathy by four times compared to those taking systemic therapy.[37] A comparison of VF progression in uveitis patients receiving steroid treatment versus those without would be of interest for future studies. Such an analysis would require accurate data on frequency, duration and formulation of steroid use, which is not routinely captured by the Medisoft EMR. Successful management of glaucoma in uveitis requires simultaneous treatment of inflammation and IOP elevation. In some cases, controlling the inflammation also helps to reduce IOP and there is evidence to suggest those treated with aggressive anti-inflammatory therapy have better outcomes.[6] Anti-glaucomatous drugs such as beta-blockers and carbonic anhydrase inhibitors can be used to lower the IOP. Some controversy exists around the use of prostaglandin analogues (PGAs) as a first-line agent due to the theoretical risk of blood-aqueous barrier disruption and cystoid macular oedema, however multiple studies have found no differences in the rate of inflammatory recurrences and it is considered safe to use PGAs as first-line therapy in quiescent uveitis.[38,39] The management options for glaucoma in uveitis are predominantly with an aim to decrease IOP, but it is unclear whether these treatments influence IOP variability.

The exact pathological process behind glaucoma in different uveitic subtypes is difficult to define, as there are often multiple co-existing mechanisms driving IOP changes and glaucomatous damage. Yet, elevated IOP has been considered the main modifiable risk factor. Our study, albeit based on retrospective data, represents the largest published longitudinal analysis of IOP behaviour in uveitis patients with glaucoma. We found the mean longitudinal IOP to be similar in uveitis and POAG. However, IOP range and MAE was higher in uveitis patients. In both uveitic and POAG groups, IOP range and MAE are consistently higher in those progressing rapidly compared to those losing less than 1.5 dB/year in MD. It is unclear whether the fluctuant IOP is a contributing factor to glaucomatous damage, or whether it is simply a more prevalent finding in those with more severe glaucoma, representing those with the poorest controlled IOP and therefore receiving the most aggressive treatment. The published literature on POAG is inconsistent in this area, with some studies reporting a strong relationship between ocular hypertension and glaucomatous field loss, whilst others suggest that long-term IOP variability is associated more strongly with progression than mean IOP.[41,42] Lee et al. suggest a 1 mmHg increase in standard deviation of IOP is associated with a four-fold increase

in risk of POAG progression.[43] In uveitis, published long-term data on IOP is limited and understanding of IOP behaviour in the context of inflammation, secondary structural damage and anti-inflammatory treatment remains poor.

Glaucoma secondary to uveitis is an important cause of irreversible sight loss, which is challenging to detect and manage. Our main finding from retrospective analysis of clinical data from multi-center glaucoma services in England shows that uveitis patients with glaucoma are almost twice as likely to lose visual field rapidly when compared to patients with POAG. Therefore, clinicians managing patients with uveitis should remain vigilant for glaucomatous damage in these high-risk patients. In England, there is evidence that most patients get a similar diet of VF examinations during follow-up, and our findings support this.[13,19] Our results at least highlight that uveitis patients require closer attention in order to rule out rapid loss of VF during treatment. IOP variability is more common in uveitic eyes and our findings suggest that IOP fluctuates across a wider range in this group than in POAG. We suggest a low threshold for glaucoma screening in patients with uveitis, even if IOP is within normal limits and particularly in the presence of a fluctuating IOP.

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C) **Authorship:** XL and SRK contributed equally and share joint first authorship. AKD and DPC share joint senior authorship.

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Figure Captions

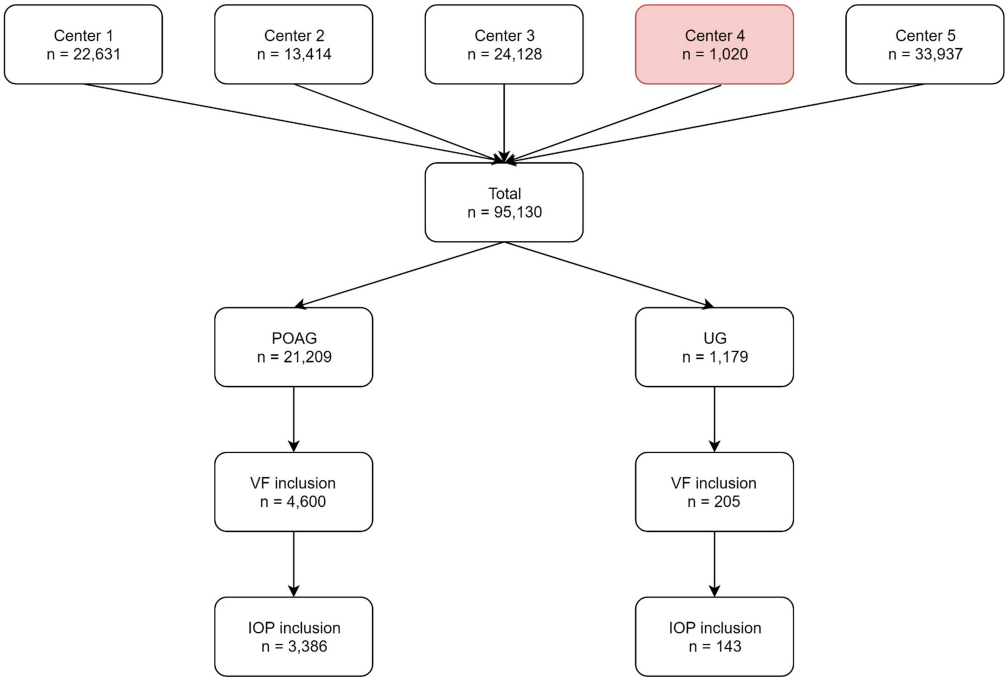
Table 1. Longitudinal IOP metrics: comparison between POAG and Uveitis plus glaucoma groups.

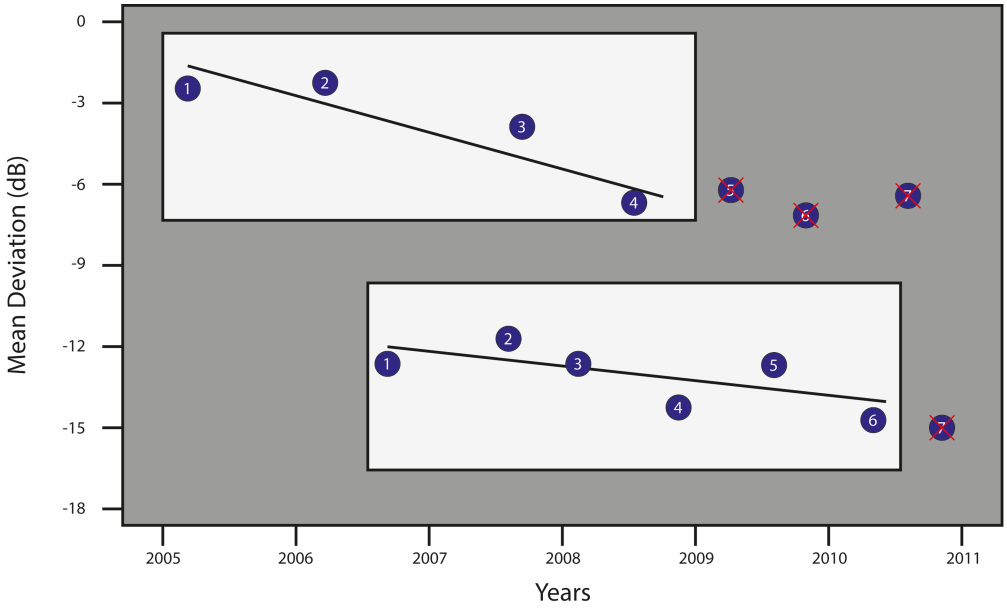
Figure 1. Flow chart showing the inclusion criteria leading to a study sample of 4,600 POAG eyes and 205 UG eyes for the VF analysis and 3,386 POAG eyes and 143 UG eyes for the IOP analysis. Number of “fast progressors” in the VF analysis are also shown. Center 4 is highlighted in red as it was missing a large amount of diagnosis data.

Figure 2. A schematic illustrating the VF series inclusion criteria and method for calculating rates of MD loss (dB/year) for two example eyes. Eyes were excluded if <4 VF examinations of <4 years of follow-up. Rates of VF loss were calculated from ordinary least squares linear regression of the baseline VF and the series of exams that fell within a 4-year window period after it (white window). In the top example, the 5th, 6th and 7th recorded VFs fall outside of the window and were not used in the calculation. In the bottom example, only the seventh exam was excluded. This ensures that all rates are estimated with equivalent precision, allowing for comparisons over time.

Table 1. Longitudinal IOP metrics: comparison between POAG and Uveitis plus glaucoma groups.

IOP (mmHg) Median (IQR)	**POAG (n=3,386)**			**Uveitis plus glaucoma (n=143)**		
Mean	16.5 (14.5, 18.8)			15.9 (13.5, 19.3)		*p* = 0.445
Range	10.5 (7.0, 15.0)			13.3 (8.0, 23.5)		***p* < 0.001**
Mean absolute error	2.1 (1.6, 2.8)			2.6 (1.9, 4.4)		***p* < 0.001**
	Normal Progressors	**Rapid Progressors**		**Normal Progressors**	**Rapid Progressors**	
Mean	16.6 (14.6, 18.6)	16.0 (13.7, 17.9)	***p* < 0.001**	15.9 (12.6, 19.2)	16.4 (12.1, 21.0)	*p* = 0.827
Range	10.0 (7.0, 15.0)	12.0 (8.5, 17.0)	***p* < 0.001**	13.0 (8.0, 22.0)	21.0 (12.0, 30.8)	***p* = 0.040**
Mean absolute error	2.1 (1.6, 2.8)	2.3 (1.7, 3.2)	***p* < 0.001**	2.6 (1.8, 2.9)	3.5 (2.3, 6.1)	*p* = 0.051





Highlights

- This study utilises real-world data from glaucoma clinics in England to investigate whether there is a difference in the rates of visual field (VF) loss between patients with primary open angle glaucoma (POAG) versus glaucoma plus uveitis?
- We found that the uveitis plus glaucoma group had a significantly higher age-corrected rate of VF progression than the POAG group.
- The age-adjusted relative risk ratio of uveitis plus glaucoma eyes for losing mean deviation ≥1.5 dB/year was 1.9 (95% CI: 1.8 - 2.0 when compared eyes with POAG only.
- Longitudinal intraocular pressure analysis showed higher IOP range and variability particularly in uveitic eyes which progress rapidly.
- Yet, median intensity of VF monitoring was the same for POAG and uveitic eyes (10 months per VF test).