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CLINICAL STUDY

Prior rates of visual field loss and lifetime risk of blindness in glaucomatous patients undergoing trabeculectomy

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Abstract

Purpose **Trend-based analyses examining rates of visual field (VF) loss in glaucoma are useful for predicting risk of vision-related morbidity. Although patients with faster losses are likely to require treatment escalation, little is known about rates that might trigger a decision to intervene surgically. The aims of this study were to investigate prior rates of VF loss in patients attending for trabeculectomy and to estimate, in the absence of surgical intervention, lifetime risk of visual impairment, and blindness.**

Patients and methods **A retrospective analysis of 117 eyes of 86 consecutive patients with glaucoma attending for trabeculectomy, including 53 patients referred from general ophthalmology clinics and 33 patients from specialist glaucoma clinics. Rates of change in standard automated perimetry mean deviation were examined using linear regression and random coefficient models. Risk of lifetime visual impairment and blindness was calculated using life expectancy data.**

Results **Mean age at surgery was 71.0 ± 9.7 years. Patients were followed for 10.7 ± 7.5 years prior to surgery with an average of seven useable fields per eye. On average patients referred from general clinics lost 1.04 dB/year compared with 0.77 dB/year in those referred from glaucoma clinics ($P = 0.070$). Patients referred from general clinics had more medication changes prior to surgery (3.4 and 2.6 changes, respectively; $P = 0.004$). Given Scottish life expectancy data, untreated, 61 eyes (52%) would have passed the threshold for visual impairment, whereas 40 (34%) would have passed the threshold demarcating blindness.**

Conclusion **Patients attending for trabeculectomy had faster average rates of field loss prior to surgery than published values for the general glaucoma population with over one-third of eyes studied predicted to have become blind without intervention. Those managed by glaucoma specialists had fewer changes in medication and tended to slower rates of VF loss, although the latter did not reach statistical significance.**

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Introduction

Calculating rates of visual field (VF) loss is an important aspect of glaucoma management as it allows the clinician to gauge an individual's lifetime risk of visual impairment and provides valuable information as to whether treatment should be escalated. Patients progressing more quickly are at higher risk of vision-related morbidity; therefore, a fast rate of VF loss is likely to lead to consideration of additional glaucoma medication or surgery. Calculation of rates of change in VF has been greatly facilitated by the introduction of software such as the Guided Progression Analysis, which includes a trend-based analysis for this purpose. However, it is only recently that investigators have explored rates of change in VF in large 'real-life' clinical cohorts.[1–4] These studies have reported average rates of VF loss in glaucoma and identified fast, moderate, slow, and non-progressors.

Guidelines such as those published by the UK NICE (National Institute for Clinical Excellence) specify that surgical intervention should be considered for patients with glaucoma 'at risk of progressing to sight loss despite treatment'.[5]

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Although calculation of rates of change in VF is an important component of estimating lifetime risk of sight loss, little is known about the rates of change that might trigger a clinician's decision to intervene surgically. The purpose of this study was to examine prior rates of VF loss in patients attending for trabeculectomy and compare these with published values for the general glaucoma population. We also examined baseline disease severity and life expectancy data in order to calculate the lifetime risk of visual impairment for eyes included in the study.

Materials and methods

This study involved a retrospective review of the medical records of patients with glaucoma attending Princess Alexandra Eye Pavilion, Edinburgh, UK. Consecutive patients undergoing first trabeculectomy from January 2009 to August 2014 were identified from operation records. The medical records were retrieved and only eyes with a diagnosis of primary open-angle glaucoma, pigmentary glaucoma, or pseudoexfoliative glaucoma were included for further analysis. Patients with primary angle-closure glaucoma, neovascular, congenital, or other forms of secondary glaucoma were excluded, as were eyes that had previous trabeculectomy. All eyes required at least three reliable VF examinations prior to trabeculectomy, with a reliable VF defined as a field with $<33\%$ fixation losses, $<33\%$ false-negative errors, and $<15\%$ false-positive errors. Visual fields showing likely artefacts such as lid or rim artefacts were excluded. Visual fields were obtained using the 24-2 SITA-Fast program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, California).

The diagnosis of glaucoma was based on the examination findings recorded in the medical notes at the time of listing for trabeculectomy. The diagnosis of primary open-angle glaucoma was made on the basis of gonioscopic examination and on the presence of glaucomatous changes to the optic nerve head or retinal nerve fibre layer, with or without the presence of glaucomatous VF changes. The diagnosis of pseudoexfoliative glaucoma was made if pseudoexfoliative material was visualised in the anterior segment at any visit. We documented whether each patient was phakic or aphakic prior to trabeculectomy, and if phakic, we recorded whether phaco-trabeculectomy was performed at the time of surgery.

The VF mean deviation (MD) was recorded for each reliable VF available prior to trabeculectomy. Other data collected from the medical records included demographic data, date of presentation (first clinic appointment at our facility), lens status, intraocular pressure (IOP) immediately prior to surgery (acquired using Goldman applanation tonometry), number of glaucoma medication changes, and total number of glaucoma medications. The number of medication changes enumerated the number of anti-glaucoma pharmaceutical changes prior to trabeculectomy. This value did not include the initiation of drug therapy (ie, a patient who received the same drug throughout the study had a score of 0). The total number of glaucoma medications referred to the number of medications being used in the operated eye when listed for trabeculectomy. Drops containing combinations of medications had each component counted separately.

Patients with glaucoma are often managed in general clinics by comprehensive ophthalmologists. At our institution, when glaucoma patients attending general clinics are deemed to have poorly controlled disease on medical treatment, or are at high risk of vision-related morbidity, referral is made to the glaucoma specialist clinic for consideration for alternative treatments including surgery. To investigate whether patients attending general clinics prior to trabeculectomy had different rates of VF loss to those attending the glaucoma clinic, we recorded the type of clinic attended by each patient as either 'general' (referred for consideration of surgery by a comprehensive ophthalmologist in the 12-month period preceding surgery) or 'glaucoma' (long-term follow-up by one of three glaucoma specialists at our institution).

We were interested to estimate the lifetime risk of blindness in our patients. To evaluate this, we defined visual impairment and blindness using similar criteria to Saunders *et al*[2] (-14 dB and -22 dB, respectively). It is important to note that unlike Saunders *et al*, we used these thresholds in the context of a single eye, rather than referring to statutory blindness. We obtained life expectancy figures from National Records of Scotland data.[6] For each eye, we calculated the age at which visual impairment and blindness would occur, given age at presentation, MD at presentation and rate of VF change.

Statistical analysis

Descriptive statistics yielded mean, SD and *t*-tests for normally distributed variables; as well as median and interquartile ranges for non-parametrically distributed variables. Rates of change in MD were calculated using linear regression analysis to allow comparison with previously published rates of VF change in the general glaucoma population.

An alternative statistical model was used to evaluate the effect of clinic type on the rate of change in MD. Here, a random coefficients model was used—a type of linear mixed model involving random intervals and random slopes. Random coefficients models have previously been used to evaluate rates of change in glaucoma.[7,8] VF MD was considered the dependent variable in this part of the

analysis. Clinic type (variable CLINIC) was included as a fixed-effect covariate with a value of 0 if the patient had attended a general clinic and a value of 1 if the patient had attended a glaucoma clinic. The variable TIME (time in years from baseline visit) was used as a continuous predictor. The significance of the coefficients of the variable TIME indicated whether there was a significant trend in change in MD over time. The interaction between CLINIC and TIME (CLINIC × TIME) was used to evaluate whether there was a significant difference in rates of change of MD over time between those patients seen in general and glaucoma clinics. Similar random coefficient models were used to evaluate the effect of possible confounding factors on rates of change in MD including baseline MD and number of medication changes prior to surgery. Statistical analyses were conducted using Stata, version 13; StataCorp LP, TX, USA.

Results

The study included 117 eyes of 86 patients. Thirty-five (40%) were male. One hundred and twelve eyes (96%) had primary open-angle glaucoma and 5 (4%) pseudoexfoliative glaucoma. Forty-five eyes (38%) were referred for surgery from a general or comprehensive ophthalmology clinic and 72 eyes (62%) from a glaucoma clinic. Table 1 shows the demographic and clinical characteristics of the two groups.

Mean age at trabeculectomy was 71.0 ± 9.7 years. Patients had been seen for an average of 11.6 ± 9.0 years prior to trabeculectomy in the general clinic and 10.2 ± 6.0 years in the glaucoma clinic ($P = 0.333$). Patients in both the general and glaucoma clinic groups had an average of seven reliable VFs available for analysis per eye. The average MD for all eyes included in the study was −7.3 dB at baseline exam decreasing to −10.1 dB at the closest VF prior to surgery (Figure 1). There was no significant difference in age, gender, follow-up period, number of VFs prior to surgery, or baseline disease severity between groups (Table 1). There was also no significant difference in lens status at baseline or the number of patients undergoing cataract surgery during follow-up between groups.

In contrast, patients referred from the general clinic had significantly more medication changes prior to surgery than those attending the glaucoma clinic (3.4 compared with 2.6 medications, respectively, $P = 0.004$). There was also a tendency for patients referred from the general clinic to be using more medications at the time of surgery

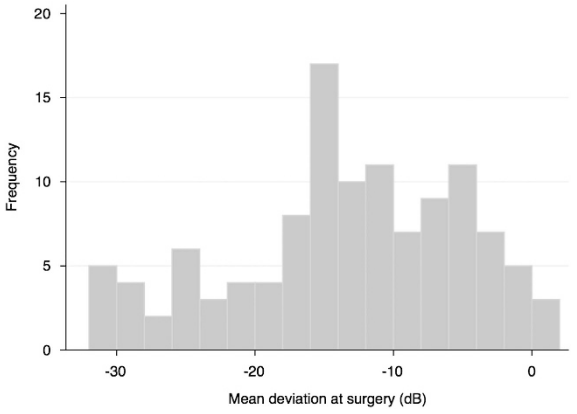

Figure 1 Histogram showing distribution of visual field mean deviation (MD) values at the closest visual field before surgery.

Table 1 Demographic and clinical characteristics of the eyes included in the study

	General clinic (45 eyes, 38.5%)	*Glaucoma clinic (72 eyes, 61.5%)*	P-*value*
Age at surgery (years)[a]	72.1 ± 8.2	70.3 ± 10.5	0.921
Gender (n)			*0.088*
Male	24 (53%)	28 (39%)	
Female	21 (47%)	44 (61%)	
Follow-up prior to surgery (years)[a]	11.6 ± 9.0	10.2 ± 6.0	0.333
VFs prior to surgery (*n*)[b]	7.0 (7, 5 to 9)	7.0 (8, 5 to 9)	0.991
Baseline MD (dB)[b]	−7.6 (−6.1, −10.4 to −2.0)	−7.1 (−4.6, −10.3 to −1.9)	0.731
MD at surgery (dB)[b]	−8.9 (−7.7, −14.3 to −1.4)	−10.9 (−9.6, −14.8 to −4.4)	0.236
Medications at surgery (*n*)[b]	2.9 ± 0.9 (3, 2 to 4)	2.6 ± 0.9 (3, 2 to 3)	0.064
Medication changes prior to surgery (*n*)[b]	3.4 ± 1.5 (3, 3 to 4)	2.6 ± 1.3 (2, 2 to 4)	0.004
IOP at surgery (mmHg)[a]	20.1 ± 4.8	20.4 ± 5.3	0.617
Baseline lens status (n)			*0.898*
Phakic	39 (87%)	66 (92%)	
Pseudophakic	6 (13%)	6 (8%)	
Cataract surgery during follow-up (*n*)	5 (11%)	8 (11%)	1.000
Phaco-trabeculectomy (*n*)	12 (27%)	16 (22%)	0.493

Abbreviations: dB, decibels; IOP, intraocular pressure; MD, mean deviation; VF, visual field. [a]Mean ± s.d. [b]Mean, (median, interquartile range).

but this did not reach statistical significance (2.9 compared with 2.6 medications, respectively, $P=0.064$).

Using linear regression, MD decreased by a median of 1.05 ± 1.23 dB/year (ranging from -7.7 dB/year to 0.57 dB/year) prior to surgery. Figure 2a shows the distribution of rates of change in MD for all eyes in the study. Figure 2b shows fitted slopes of change in MD for all eyes. According to the criteria defined by Kirwan *et al*,[1] 15 of 117 eyes (13%) were 'fast progressors' with VF progression > -2 dB/year, 28 eyes (24%) were 'moderate progressors' with progression between -1 and -2 dB/year, 46 eyes (39%) were 'slow progressors' with progression between -1 and -0.3 dB/year and 28 eyes (24%) were 'non-progressors' with changes of > -0.3 dB/year.

Life expectancy data from the National Records of Scotland indicated life expectancy at birth of 77.4 years for males and of 81.9 years for females.[6] Using our definitions of visual impairment (−14 dB) and blindness (−22 dB) we calculated that of the 117 eyes in the study, if VF progression had continued at similar rates, 61 (52%) would have passed the -14 dB threshold for visual impairment, whereas 40 (34%) would have passed the -22 dB threshold demarcating blindness.

Table 2 shows the results of the random coefficients model investigating the relationship between rate of change of MD and clinic type. In this model, the rate of change in patients attending the general clinic was -1.04 dB/year (coefficient of variable TIME), whereas the rate of change in the glaucoma clinic was -0.77 dB/year (sum of coefficient of variable CLINIC by TIME and coefficient of variable TIME). This difference did not reach statistical significance ($P=0.070$). Similar random coefficients models were used to examine the effect of other possible variables on rates of VF loss prior to surgery. There was no significant effect of age ($P=0.056$), baseline MD ($P=0.842$), or number of medication changes ($P=0.288$) on rates of change. Those patients taking higher numbers of anti-glaucoma medications at time of surgery had not experienced faster rates of VF loss ($P=0.102$). We also examined rates of change in MD in those having combined cataract surgery and trabeculectomy versus trabeculectomy alone but found no significant difference (-1.02 ± 0.86 dB per year versus -1.05 ± 1.33 dB per year, respectively, $P=0.509$).

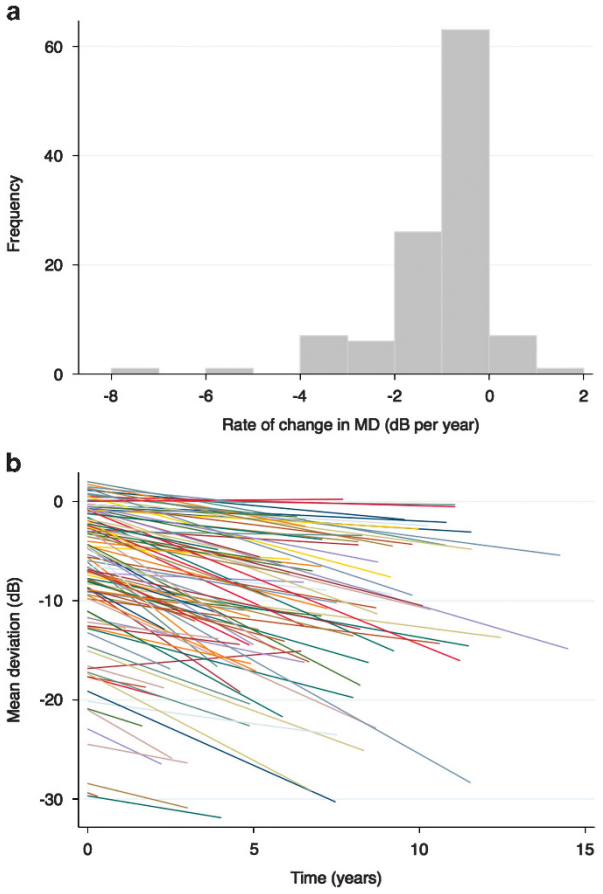

Figure 2 (a) Histogram showing the distribution of rates of visual field loss for all eyes included in the study. (b) Line graph showing fitted slopes of change in MD for all eyes included in the study.

Table 2 Results of the random coefficients model examining the association between rate of change in visual field mean deviation and clinic type

Parameter	*Coefficient*	*95% CI*	P-*value*
TIME (years)	−1.04	−1.29 to −00.80	0.000
CLINIC	1.34	−1.74 to 4.41	0.395
CLINIC × TIME	0.27	−0.03 to 0.58	0.070

Abbreviations: 95% CI, confidence interval; CLINIC × TIME, interaction between clinic type and variable TIME; TIME, duration of follow-up.

Discussion

In this study we examined prior rates of VF loss in patients with glaucoma attending for trabeculectomy. On average there was 1.05 ± 1.23 dB/year deterioration in MD over an average follow-up of almost 11 years preceding surgery. Although factors including baseline disease severity, IOP, family history of glaucoma and glaucoma blindness, and life expectancy are also likely to influence risk of visual impairment and the decision to escalate treatment, the results of the study provide an indication of the rates of VF loss that might trigger a clinician to consider surgery.

Previous studies in real-life clinical cohorts have reported a typical rate of VF loss of only 0.1–0.5 dB/year.[1,2,4,9–14] The average rate of deterioration in our patients was significantly faster, which is to be expected as our cohort was restricted to patients

Table 3 Comparison of the percentage of eyes progressing at different rates in our study with the results of Kirwan *et al*[1]

	Our results (%)	*Kirwan* et al *(%)*
Fast progressors (VF loss worse than 2 dB/year)	12.8	2.1
Moderate progressors (1–2 dB/year)	23.9	7.3
Slow progressors (0.3–1 dB/year)	39.3	22.5
Non-progressors (<0.3 dB/year)	23.9	65.9

undergoing glaucoma surgery. However, despite the fact that, overall, eyes undergoing trabeculectomy progressed at faster rates than reported for the general glaucoma population, we found a large variation in rates of VF change. Furthermore, we showed that some patients had no deterioration on available VFs. Using the taxonomy of Kirwan *et al*, 36.7% of eyes in our cohort were fast or moderate progressors compared with only 9.4% of Kirwan *et al*'s cohort of general glaucoma patients. In total, 23.9% of eyes in our study were non-progressors compared with 65.9% in Kirwan *et al* cohort (Table 3).[1] We also had proportionally more fast progressors than Chauhan *et al*, who in a study of 2324 eyes reported only 1.5% of eyes as having a progression rate of faster than 2 dB/year, eyes they labelled as catastrophic progressors.[4] Similarly, Saunders *et al* found only 3% of glaucomatous eyes lost >1.5 dB/year.[2]

Our results indicate that a large proportion of patients (almost one quarter) attending for trabeculectomy had no significant progression in MD documented. Further review of the case notes for the apparently slow or non-progressing patients revealed the main indications for trabeculectomy to be suboptimal control of IOP despite medical treatment or intolerance to topical medications. In 10 out of 28 non-progressing eyes (36%), the patient had had previous trabeculectomy in their fellow eye, and a good surgical outcome may have lowered the threshold for surgery in the second eye. Furthermore, although eyes may have shown slow or no recent progression, non-progressing eyes already had significant VF loss with an average MD of –8.5 dB, which may have necessitated lower target IOP.

Previous studies reporting rates of VF loss in the general glaucoma population (on treatment) have suggested only a minority of patients with glaucoma are fast progressors. Kirwan *et al* found only 2% of patients lost >2 dB/year, with other studies showing only 1.5–15% of patients have a rate of progression exceeding 1.5 dB/year.[3,4,15–17] We favoured the taxonomy proposed by Kirwan *et al* to group rates of VF progression, as it represents a large clinical audit of glaucoma progression conducted in the United Kingdom.[1] Nevertheless, it is important to emphasise that a direct comparison of progression rates is likely—to some degree—to be confounded by variation in the demographics of included subjects. The high proportion of fast progressors reported in the Swedish population exposes the large variation in rates of VF deterioration between geographical regions, and highlights the importance of population demographics in determining rates of progression.[18] A previous study from Belgium, which examined rates of VF loss in 52 eyes before and after trabeculectomy, reported an average loss of only 0.36 dB per year before surgery.[14] However, this study included patients with angle-closure and secondary glaucomas and 42% of eyes had surgery for raised IOP rather than VF progression. Furthermore, patients in our study had longer follow-up and more VF examinations prior to surgery.

Important factors to consider when determining whether a rate of progression is 'significant for the patient' include disease severity at baseline, age, and an estimate of life expectancy. Without this information, progression rates alone provide insufficient information for clinical decision-making. A young patient with early disease progressing slowly could have a higher lifetime chance of developing significant visual impairment than an older patient with worse disease and a faster rate of progression. The Early Manifest Glaucoma Trial demonstrated median rate of MD deterioration in untreated patients with primary open-angle glaucoma to be slower than −0.5 dB/year. At this rate, it would take ~70 years to progress from normal visual function to blindness.[9] Our data indicated that, if VF progression had continued at similar rates, 52% of eyes would have passed the −14 dB threshold for visual impairment, whereas 34% of eyes would have passed the −22 dB threshold demarcating blindness.

Hattenhauer *et al*[19] conducted a retrospective descriptive study of 295 patients with primary open-angle glaucoma, with the aim of determining the probability of developing legal blindness over 20-year follow-up. The authors found the cumulative probability of glaucoma-related blindness in at least one eye to be 27%. Our figure of 34% is likely a reflection of severe disease at baseline, as well as the relative high proportion of fast and medium progressors within our cohort, which is expected given that these patients were attending for glaucoma surgery.

The NICE guidelines recommend that surgery should be offered to patients with glaucoma who are at risk of progressing to sight loss despite treatment.[5] By calculating rates of change in VF using trend-based analyses it is possible to estimate this risk. The guidelines further specify that surgery should be considered after two failed pharmacological treatments. We found an average of 2.9 changes in medication prior to surgery, which is higher than that recommended by NICE. Notably, the number of medication changes was

significantly greater in those attending the general compared with glaucoma clinic (3.4 compared with 2.6, respectively, $P=0.004$). This could feasibly be due to glaucoma specialists having a lower threshold for considering surgery compared with general ophthalmologists. A further interesting observation was the tendency (although not statistically significant, $P=0.070$) for patients seen in general clinics to have had faster rates of VF deterioration than those seen by glaucoma specialists (losses of 1.04 dB/year and 0.77 dB/year, respectively). As there were no significant differences in age, glaucoma-type, or baseline disease severity between groups, one might suppose that the faster rates of progression in the general clinic group could be due to suboptimal control of IOP; however, further studies would be needed to corroborate this.

This study has limitations. It is possible that concomitant age-related eye disease, particularly cataract, may have contributed to faster VF progression in some patients.

One hundred and five of 117 eyes (89.7%) were phakic prior to surgery and 28 eyes (23.9%) had concurrent cataract extraction at the time of trabeculectomy, suggesting cataract may have partly contributed to deterioration in visual function. However, there was no significant difference in lens status at baseline or the number of patients undergoing cataract surgery during follow-up in the general compared with the glaucoma groups. There was also no significant difference in the number of patients undergoing phaco-trabeculectomy. In some eyes with coexistent cataract and glaucoma, the decision for combined surgery may have been influenced by a desire to improve vision rather than concern about glaucoma progression. However, inclusion of these cases would have the effect of reducing the overall rate of VF loss in our study group, and therefore would not detract from our main conclusion that patients attending for trabeculectomy exhibit faster rates of VF decline compared with the wider glaucoma population. Use of visual field index rather than MD may have helped minimise the effect of cataract but due to the retrospective nature of the study visual field index data was not available for older VFs. It is important to acknowledge that for some eyes included in the study, poor performance on standard automated perimetry may have triggered the decision to proceed with surgery, despite being an inaccurate representation of the underlying rate of VF deterioration. That is to say, in these cases, the measured rate of VF change may be an overestimation of the true rate. The advantage of retrospective design is that our data reflects routine clinical care. In contrast, volunteer patients in prospective glaucoma trials have been shown to have better adherence than patients in routine care, hence affecting external validity.[20] A further limitation of the study is that we did not investigate localised VF changes. Some patients may show localised VF progression with minimal change in global indices such as MD. Localised change, particularly progression threatening fixation, may prompt the decision for surgery. However, the aim of this study was to examine rates of change in a global VF index, as linear regression of global indices is used in clinical practice to examine rates of change in trend-based analyses and for the estimation of lifetime risk of visual impairment. A limitation of the lifetime visual impairment estimates we calculated was that individual comorbidities were not accounted for, and that estimates did not take account of patient age. We also assumed a linear rate of change in MD, which is questionable given the non-linear decibel scale used in VF analyses. However, a study conducted by Bengtsson and Heijl has found linear extrapolation based on VF test results to be a reliable predictor of future field loss in most patients.[21] Furthermore, this approach reflects current clinical practice.

Despite the above limitations, this study shows that, on average, patients attending for trabeculectomy had faster rates of VF loss preceding surgery than rates reported for the general glaucoma population. The lifetime risk of blindness for these patients was also higher than reported for the wider glaucoma population, with more than a third of patients predicted to have become blind in the affected eye if field loss continued at a similar rate. Although patients had a large number of medication changes prior to surgery, the number of medication changes was not associated with rate of VF loss. However, patients seen initially by glaucoma specialists tended to have fewer medication changes and slower rates of VF loss prior to surgery.

Summary

What was known before

- Glaucoma progression is typically examined using event-based and trend-based analyses of visual fields.
- Trend-based analyses are important as patients with fast rates of change are at higher risk of lifetime visual loss.
- Although previous studies have evaluated rates of VF loss in the general glaucoma population, to our knowledge none have examined rates of VF deterioration among patients attending for glaucoma surgery – in other words the rate of field loss likely to prompt a clinician to recommend surgical treatment.

What this study adds

- It enumerates rates of VF deterioration in glaucoma patients undergoing glaucoma surgery.
- It reviews the literature regarding rates of VF loss in glaucoma.
- It compares rates of change in those attending general and specialist ophthalmologists with reference to NICE guidelines.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

AJT had the original idea for the study, performed the statistical analysis and contributed to the writing of the manuscript. WSF was involved in study design, collected the data, contributed to the analysis and was the main author of the manuscript. LF was involved in the study design, collected the data and contributed to the writing of the manuscript.

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