Validation of the RCOphth and UKEGS Glaucoma Risk Stratification Tool “GLAUC-STRAT-fast”.

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Synopsis

This paper validates the 'GLAUC-STRAT-fast' glaucoma risk stratification tool; the tool appears to be useful for the risk stratification of glaucomatous eyes, but could benefit from further refinement and validation.

Abstract

Background/Aims: The aim of this study was to validate the Glaucoma Risk Stratification Tool (GLAUC-STRAT-fast) currently recommended by the UK Royal College of Ophthalmologists for the risk stratification of patients with glaucoma in the NHS Hospital Eye Service (HES).

Methods: GLAUC-STRAT fast was applied to the LiGHT trial participants by risk-stratifying the worse eye of each patient at baseline and after 3 years of treatment. Metrics of disease severity or treatment intensity used for the validation were: increased number of monitoring visits or treatment escalations; needing a trabeculectomy; a reduction of >2~~dB~~dB in visual field mead deviation (VF MD) during the monitoring period ~~(VF)~~; identification of rapid visual field loss on total (TD) and/or pattern deviation (PD). The proportion of eyes within each baseline stratum for each of the above markers was compared against the other strata, using a chi square test for proportions.

Results: There was an association between the baseline stratification and the number of treatment escalations needed to maintain the eye-specific target IOP (p=0.001), the number of visits needed throughout the 3-year follow-up period (p=0.001), the need for trabeculectomy (p<0.001) and absolute loss of MD over the course of the monitoring period (p<0.001). The rate of VF progression was not associated with baseline risk stratification for TD or PD progression (p≥0.007, with Bonferroni correction).

Conclusion: The GLAUC-STRAT fast tool is a useful tool for risk stratifying eyes with OHT or open angle glaucoma. Further research is needed to confirm its applicability to more severe patient groups and generalisability to clinical use.

INTRODUCTION

Glaucoma is a leading cause of visual impairment (VI) in the UK, requiring regular monitoring by specially trained eye-care professionals. Despite a recent decrease in VI certifications related to age-related macular degeneration and diabetic retinopathy, the certification rate for glaucoma has remained unchanged [1]. There are reports of severe vision loss attributed to the lack of capacity for timely monitoring of patients with glaucoma within the Hospital Eye Service (HES).[2,3] Monitoring of glaucoma patients has been further hindered by the COVID-19 pandemic, during which almost 30,000 glaucoma outpatient attendances were deferred at Moorfields Eye Hospital.[4]

To address the lack of capacity in the glaucoma services nationwide, new models of care have been proposed; community glaucoma monitoring schemes, improved referral refinement, management of glaucoma patients by appropriately trained non-medical professionals and the risk stratification of glaucoma patients have been proposed.[5-8] The Healthcare Safety Investigation Branch has recommended further research into the development and evaluation of risk stratification tools, which would allow tailoring follow-up appointments to the patients' clinical needs, whilst enabling the standardisation of practice across the NHS.[8]

The Glaucoma Risk Stratification Tool (GLAUC-STRAT) was adopted by the Royal College of Ophthalmologists (RCOphth) and the UK and Éire Glaucoma Society (UKEGS), for use as a stratification tool in the NHS glaucoma clinics but is yet to be supported by published validation studies. The LiGHT trial cohort includes carefully curated clinical data from 718 patients (1235 eyes) diagnosed with open-angle glaucoma (OAG) or ocular hypertension (OHT), spanning more than 3 years. The aim of this study was to validate the Glaucoma Risk Stratification Tool adjusted for the NHS (GLAUC-STRAT-fast), using the LiGHT trial patient cohort.

METHODS

The joint RCOphth and UKEGS Glaucoma Risk Stratification Tool

GLAUC-STRAT is a clinical tool, initially developed by Shal et al,[9] subsequently adjusted to facilitate use in the NHS (GLAUC-STRAT-fast), and currently recommended by the RCOphth and UKEGS for the risk stratification of patients with glaucoma. The tool classifies patients into strata of risk that aim to predict the risk of significant sight loss in the future and to estimate the resource requirements for patient management.[10] The tool is largely reliant on visual field mean deviation (VF MD) and adopts a Red-Amber-Green stratification as three main diagnostic categories; each category is divided to 3 sub-strata, depending on the presence of 'red flags' and/or 'plus factors' (Figure 1). The tool considers diagnosis, stage and complexity of disease, rate of VF progression, life expectancy, ocular and systemic

comorbidities, dependency and socio-economic deprivation; each patient is stratified based on their worse eye.

Analysis cohort

The GLAUC-STRAT-fast tool was validated against the LiGHT trial cohort. Details of the LiGHT trial cohort have been described in detail elsewhere.[11] Briefly, the LiGHT trial was a multicentre, randomised controlled trial comparing selective laser trabeculoplasty (SLT) with IOP-lowering eye drops in 718 newly diagnosed, previously untreated OHT or OAG patients. Patients randomised to drops received IOP-lowering eye drops to reduce IOP, whereas patients randomised to laser underwent SLT (followed by medication if required). Each eye was treated to a specific IOP target that was defined by a computerised decision support software (algorithm).[12,13] Treatment escalations were conducted according to the study protocol following an algorithm decision, to avoid bias in clinical decision making.

Baseline stratification

The worse eye of each patient was stratified based on baseline demographic and ocular characteristics, as described by GLAUC-STRAT-fast. Central field loss was identified according to Mills et al,[14] as having at least 1 point within central 5° with sensitivity <15 dB in the baseline VF. Baseline characteristics for the included eyes are presented in Table 1; a total of 713 eyes were included in the study (5 were excluded due to limited follow-up data).

Age (years)	63.7
(median, IQR)	(53.9, 72.0)
Gender	
Female (N, %)	320 (44.9%)
Male (N, %)	393 (55.1%)
VF MD (dB)	-3.0
(median, IQR)	(-19.28, 2.18)
LiGHT diagnosis	
OHT	186 (26.1%)
Mild OAG	345 (48.4%)
Moderate OAG	116 (16.3%)
Severe OAG	66 (9.3%)
GLAUC-STRAT-fast condition	
OHT Tx	179 (25.1%)
2° OHT	7 (1.0%)
Early OAG	341 (47.8%)
2° OAG <4 dB	4 (0.6%)
Moderate OAG <3 drops	114 (16%)
2° moderate OAG	2 (0.3%)
Advanced OAG	65 (9.1%)
2° advanced OAG	1 (0.1%)
VF loss within the central 5° (N, %)	67 (9.4%)

Table 1 *Baseline characteristics of included patients and eyes. 2°: secondary. OAG: Open Angle Glaucoma. OHT: Ocular Hypertension. 2° OHT and 2° OAG were due to pseudoexfoliation. 2° OAG <4dB: secondary OAG with a VF MD <4dB. Moderate OAG <3 drops: Moderate OAG treated with fewer than 3 drops.*

Due to the nature of the LiGHT trial cohort,[11] i.e. treatment naïve OAG/OHT patients with no ocular co-morbidities, the following GLAUC-STRAT *red flags* and *plus(+) factors* were not applicable for the stratification of patients at baseline: angle closure glaucoma, more than 2dB loss in a single year, unexplained visual acuity loss, IOP ~~greater than~~ ≥40mmHg, current/multiple drug reaction, ocular/periocular tumour, uveitis, significant retinal disease, previous glaucoma surgery, mental disability.

Validation

Each eye was stratified at baseline and after 3 years; monitoring and treatment during the 3-year trial period were done according to the LiGHT trial protocol.[12] To validate the GLAUC-STRAT tool, clinical outcomes after at least 3 years of treatment were utilised. Specific markers of disease management and progression, aligned with the tool's aims, were used. These were:

- Being outside the inter-quartile range for visits during the first 3 years of treatment
- Being outside the inter-quartile range for treatment escalations during the first 3 years of treatment
- Needing a trabeculectomy within the first 3 years of treatment
- A reduction of >2dB in MD at the last available visual field (VF) (up to 6.1 years) compared to baseline
- Identification of fast TD and/or PD progression (up to 6.1 years)

The proportion of eyes within each baseline stratum for each of the above markers was compared against the other strata, using a chi square test for proportions. Due to multiple testing (n=7), a Bonferroni correction was applied and the final significance level was 0.007. Analysis was conducted using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Visual field progression analysis

Categorisation to fast VF progression was done according to Wright et al.[15] A longitudinal series of VFs was constructed for each eye; 1178 eyes from 688 patients were available for analysis and only the worse eye of each patient was used for this study. Median follow-up time was 48.7 months and median VF series length was 9 VFs. Change was examined at each location in each VF series, excluding the blind spot; eye-level variation and between-eye correlation were accounted for in the original analysis. Two outcome variables were extracted from the VF analyser and modelled: total deviation (TD, the difference of the measured sensitivity at each location from what is expected for a healthy, age-matched patient) and pattern deviation (PD, the TD value at each location adjusted for any generalised depression of sensitivity across the VF).[16] Fast progression was characterised as a loss of more than 1 dB/year.

All LiGHT trial participants had provided written informed consent before participation. The LiGHT trial is registered at controlled-trials.com (ISRCTN32038223).

RESULTS

Stratification at baseline revealed 415 eyes (58.2%) stratified as Green, 191 eyes (26.8%) stratified as Amber and 107 eyes (15%) stratified as Red (Figure 2)

Disease management

There was an association between the baseline stratification and the proportion of patients requiring an increased number of treatment escalations to maintain the eye-specific target IOP. In total, 9.9% (41) of eyes stratified as Green, 17.8% (34) of eyes stratified as Amber and 22.4% (24) of eyes stratified as Red needed treatment escalations that fell outside the IQR range (0 to 2) of the LiGHT cohort treatment escalations during the course of the 3-year trial (χ^2(2, N=713)=14.6, p=0.001) (Figure 3).

The proportion of patients requiring an increased number of visits throughout the 3-year follow-up period was also associated with the baseline stratification of the study eyes; 16.4% (68) of eyes stratified as Green, 18.3% (35) of eyes stratified as Amber and 32.7% (35) of eyes stratified as Red needed a number of visits that fell outside the IQR range (7 to 12) of the LiGHT cohort visits over 3 years (χ2(2, N=713)=14.7, p=0.001) (Figure 3).

Baseline risk stratification was associated with the need for trabeculectomy; a total of 6 eyes (5.6%) stratified as Red needed a trabeculectomy within the first 3 years of diagnosis, compared to 3 eyes stratified as Amber (1.6%) and 1 eye stratified as Green (0.2%) (χ^2(2, N=713)=14.8, p<0.001) (Figure 3).

Progression of VF

Absolute loss of MD over the course of the period for which the VF analysis was conducted (median 48.7 months) was associated with baseline risk stratification; 6% (25) of eyes stratified as Green, 18.3% (35) of eyes stratified as Amber and 33.6% (36) of eyes stratified as Red lost more than 2~~db~~dB over the course of the monitoring period despite treatment (χ^2(2, N=713)=60.9, p<0.001) (Figure 4).

The proportion of fast-progressing eyes was not associated with baseline risk stratification for TD progression ((χ^2(2, N=713)=4.4, p=0.11) and was borderline statistically significant for PD progression (χ^2(2, N=713)=9.9, p=0.007). For PD progression, however, the association did not follow a trend for an increasing rate across stratification groups (χ^2(1, N=713)=2.8, p=0=0.1); 3.1% (6) of eyes stratified as Amber demonstrated fast PD progression, compared to 0.2% (1) of eyes stratified as Green and 0.9% (1) of eyes stratified as Red (Figure 4).

Change of stratification over 3 years

After 3 years of treatment and monitoring according to the LiGHT trial protocol, 74.9% (311) of the eyes initially stratified as Green, 45.5.% (87) of the eyes initially stratified as Amber and 80.4% (86) of the eyes initially stratified as Red maintained the same GLAUC-STRAT stratum (Figure 5).

Of the eyes stratified as Green at baseline, 25% had a worse stratification after 3 years; 21.4% (89) were stratified as Amber and 3.6% (15) were stratified as Red at the end of the trial. Of those, 17.3% (18) were diagnosed with OHT at baseline and 83.7% were diagnosed with mild OAG at baseline, according to the LiGHT trial disease classification.

Of the eyes originally stratified as Amber, 27.7% (53) were stratified as Red at the end of the trial; of those, 39.6% (21) were diagnosed with OHT or mild OAG at baseline, according to the LiGHT trial disease classification. Of the eyes originally stratified as Amber, 26.7% (51) were stratified as Green at the end of the 3-year monitoring period. Of the eyes originally stratified as Red, 14.0% (15) were stratified as Amber and 5.6% (6) were stratified as Green at the end of the trial.

DISCUSSION

Ophthalmology appointments account for more hospital outpatient activity than any other speciality. In 2017 approximately 20% of these were attributable to monitoring and treating patients diagnosed with glaucoma with more than 50% of glaucoma consultants reporting service backlogs, in some cases leading to irreversible sight loss.[6,17] In response to the increased burden on glaucoma services and its consequences, the RCOphth and UKEGS now recommend the use of the GLAUC-STRAT risk stratification tool for glaucoma.

This study aimed to validate GLAUC-STRAT fast against the LiGHT trial cohort, a carefully monitored group of patients with reliable VF progression, detailed clinical data and known clinical status after at least 3 years of protocolised IOP-lowering treatment.18 The LiGHT trial recruited patients referred from primary care to the NHS for the investigation of OAG or OHT; these conditions represent the bulk of cases this tool is applicable to (e.g. OAG represented 15 times the volume of angle closure patients in the HES between 2019-2020),[19] with rates of angle closure glaucoma consistently reducing due to current practice and treatment options. [20,21]

GLAUC-STRAT is an MD-driven stratification tool, resulting in a Red-Amber-Green stratification of eyes diagnosed with glaucoma. Utilisation of MD for an informal risk stratification of glaucomatous eyes has long been used in daily clinical practice, but also for glaucoma severity classification.[14] Despite its ease of use and the familiarity of clinicians with MD there are limitations to its use. An improvement

due to learning effects is now known to persist even after 10 or more tests,[22,23] with some studies reporting a positive rate of change in MD for nearly half the study population;[24] in addition MD also improves after cataract surgery. –VF improvement has also been reported after IOP lowering treatment, as it has been purported that ganglion cells may regain their function following effective treatment.[25] In this study more than 20% of eyes demonstrated an improvement in VF MD at the end of the monitoring period, which is attributable to the above factors. A detailed consideration of how an apparent improvement of stratification may impact on the applicability of such stratification tools is necessary for their efficient and safe use.

The analysis presented here, demonstrates a reasonable performance of the GLAUC-STRAT fast tool in risk stratifying eyes newly diagnosed with OHT or mild to moderate OAG. Eyes stratified as Red at first diagnosis were associated with a higher number of treatment escalations to maintain an eye-specific target IOP, set according to the Canadian Target IOP Workshop.[26] Eyes with more advanced disease at diagnosis are likely to require lower target IOP to slow the progression of glaucoma[27] and are indeed more likely to require further interventions. The National Institute for Health and Care Excellence (NICE) recommends that patients presenting with newly diagnosed advanced OAG should be offered trabeculectomy as an initial treatment[28] and the Treatment of Advanced Glaucoma Study (TAGS) recently reported that initial trabeculectomy in eyes with advanced OAG achieved lower IOP compared to eye drops.[29] In this study, eyes stratified as Red were also associated with higher rates of incisional glaucoma surgery, although only a small number of eyes in the LiGHT trial needed surgery in the first 3 years post diagnosis. Despite late presentations of glaucoma gradually reducing in England, up to 39% of patients first presenting in the HES may demonstrate severe VF loss in at least one eye.[30,31] Stratification tools that can help quickly and successfully identify patients at a greater need for glaucoma surgery can be very valuable at allocating appropriate resources.

GLAUC-STRAT fast is a reasonable predictor of risk for mild/moderate disease but may not be adequate to be used in isolation. Although there was an association of baseline stratification and absolute loss of MD, GLAUC-STRAT fast did not identify eyes that exhibited fast TD or PD progression. VF progression data were available for a median period of 4 years and have previously been used to identify a slower rate of VF loss in eyes initially treated with selective laser trabeculoplasty (SLT) compared to eye-drops.[15] Although a small proportion of eyes in this study were classified as fast progressors, it is possible that GLAUC-STRAT fast may not adequately predict which patients are likely to deteriorate faster.

In this study, fast progressing eyes were identified as losing more than 1dB per year according to studies of glaucoma progression in large clinical populations.[15,32,33] A large UK hospital-based study

reports that only 2% of eyes progress faster than 2 dB/year.[34] GLAUC-STRAT fast considers the loss of more than 2dB in a single year as a 'Red Flag'. Based on the currently available data it is likely that a loss of 2dB per year may not be sensitive enough to timely identify eyes at risk of losing functional vision. Nevertheless, the balance between identifying rapidly progressing eyes and the resource needs of slower progressing eyes needs to be considered.

Consideration must also be given to the reasons behind fast progression; the LiGHT trial cohort used to validate GLAUC-STRAT fast was treated to target IOP throughout the monitoring period; nevertheless some patients showed a fast VF deterioration.[15] Predicting fast VF progression is not straightforward, with recent reports indicating that baseline glaucoma severity does not influence the rates of RNFL and GCL thickness change.[35] Patients' genetic profile might be more beneficial when attempting to predict which patients will progress faster.[36] These findings must be accounted for when adopting risk stratification tools for use in the NHS and its service design and delivery.

GLAUC-STRAT fast also identifies central VF as an automatic Amber stratification criterion, irrespectively of MD. As part of this analysis central VF loss was initially characterised as a) baseline VFs with any 1 point within the central 5° having a pointwise p<0.05 associated with TD and/or PD, according to West et al [37], and b) baseline VFs with at least 1 point within the central 5° with sensitivity of <15 dB, according to Mills et al.[14] The two approaches yielded markedly different outcomes; identification based on any central point having a p<0.05 proved non-specific, as nearly half the eyes included in the analysis cohort demonstrated at least 1 such point at baseline. Identification of central loss based on at least 1 central point within the central 5° with sensitivity of <15 dB identified 68 eyes, exclusively stratified as Amber or Red at baseline. Additional clarity on central loss is needed for the accurate application of this tool, whilst keeping in mind the effect of central loss of vision on the patients' quality of life and vision-specific dependency[38]

When trying to link a stratification tool to available clinical data other factors may need to be accounted for. Older age is associated with more rapid progression of the disease~~,~~[39] and the risk of sight loss includes a life expectancy component; this is~~,~~ currently not included in GLAUC-STRAT fast. Family ocular history of glaucoma is also an important risk factor and should be considered, but the weight this should carry is uncertain. Recently a prediction model was applied to the Ocular Hypertension Treatment Study (OHTS 3).[40] The model accounted for baseline age, IOP, central corneal thickness, vertical cup-disc ratio and VF pattern standard deviation; baseline categorisation into low-, medium-, and high-risk tertiles led to 20-year cumulative incidences of POAG representative of the baseline risk groups. Future such tools must be able to automatically incorporate metrics of optic nerve head, nerve fibre layer and macular imaging, rates of VF change, as well as information from

electronic patient records. The use of retrospective data can prove very useful in refining such tools and validating their clinical effectiveness.

Refinements of this tool could be able to identify patients suitable for less intense monitoring; data from the English HES service indicate that less than 20% of OHT patients convert to POAG over a 5-year period, suggesting some groups may require less intensive follow-up.[41] Future sub-group refinements of such tools could also prove useful and further allow the adjustment of HES resources depending on disease characteristics (e.g. OHT, angle closure, secondary glaucoma). However, the stability of the risk presented in this study (nearly 3/4 of Green and Amber eyes) is a result of a careful, algorithm-based follow-up,[12] whilst despite this monitoring regime approximately 25% of the Green and Amber eyes still deteriorated based on GLAUC-STRAT. The timing and frequency of follow-up may affect the outcome of treatment and is directly linked to GLAUC-STRAT's aim to prioritise care. Therefore, the application of any risk stratification tools and the decision making based on their use require careful consideration.

This study represents a retrospective exploratory analysis and was not prospectively designed to validate the accuracy of the GLAUC-STRAT tool, whilst the clinical markers against which the tool was validated were chosen by the research group to flag significant future sight loss and to estimate the resource requirements for patient management. This analysis demonstrates a reasonable performance of the GLAUC-STRAT tool in risk stratifying eyes with OAG or OHT and in identifying an association of baseline stratification with indices of HES utilisation and cost. Despite a limited case-mix included in this validation (predominantly OHT, mild and moderate OAG) the patients participating in the LiGHT trial represent the bulk of patient referred to and seen in the glaucoma HES. The longstanding backlogs of the glaucoma services, exacerbated by the COVID-19 pandemic, have highlighted the need for glaucoma risk stratification tools, which will need to be carefully validated for patients that will benefit most.

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AUTHOR CONTRIBUTION STATEMENT

EK designed the work acquired and analysed data, interpreted the results and wrote the manuscript.

AK designed the work acquired and analysed data, interpreted the results and revised the manuscript.

HJ and GG conceived and designed the work, interpreted the results and revised the manuscript.

CONFLICT OF INTEREST

Professor Gus Gazzard is the president-elect of UKEGS.

FUNDING STATEMENT

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Figure legends

Figure 1 *The GLAUC-STRAT-Fast tool, representing current RCOphth/UKEGS Guidance (10).*

Figure 12 *Baseline stratification of the LiGHT trial cohort (one eye of each patient) using the GLAUC-STRAT-fast tool; 58.2% of eyes were stratified as Green, 26.8% were stratified as Amber and 15% were stratified as Red.*

Figure 23 *Proportions of eyes stratified as Green, Amber and Red at baseline, needing increased number of treatment escalations, increased number of visits and trabeculectomy over the 3-year monitoring period from diagnosis.*

Figure 34 *Proportions of eyes classified as Green, Amber and Red at baseline, losing more than 2dbdB ($\chi^2(2, N=713)=60.9$, $p=0<.001$) and demonstrating fast TD and PD progression rates according to Wright et al[15] ($\chi^2(2, N=713)=4.4$, $p=0.11$) (PD $\chi^2(2, N=713)=9.9$, $p=0=0.007$) .*

Figure 45 *Stratification after 3 years of monitoring and treatment, categorised by baseline stratification. Of the eyes stratified as Green at baseline, 74.9% were stratified as Green, 21.4% were stratified as Amber and 3.6% were stratified as Red at the end of the 3-year monitoring period. Of the eyes stratified as Amber at baseline, 26.7% were stratified as Green, 45.5% were stratified as Amber and 27.7% were stratified as Red at the end of the 3-year monitoring period. Of the eyes stratified as Red at baseline, 5.6% were stratified as Green, 14% were stratified as Amber and 80.4% were stratified as Red at the end of the 3-year monitoring period.*

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