Early Detection of Potential Non-responders to Selective Laser Trabeculoplasty in Open-Angle Glaucoma

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Abbreviations:

AUROC = area under the receiver operating characteristic curve; BS = baseline; CCT = central corneal thickness; CI = confidence interval; FP = follow-up; HRT = Heidelburg retinal tomography; IOP = intraocular pressure; LiGHT = Laser in Glaucoma and Ocuar Hypertension Trial; LR = logistic regression; MD = mean deviation; NS = non-responders; OAG = open-angle glaucoma; PSD = pattern standard deviation; ROC = receiver operating characteristic curve; SD = standard deviation; SLT = selective laser trabeculoplasty; VA = visual acuity; VF = visual field.

Key Words: selective laser trabeculoplasty; open-angle glaucoma; non-responders; predictive models; machine learning

Abstract

Purpose: To investigate the characteristics of non-responders to selective laser trabeculoplasty (SLT) and develop interpretable models for early detection of non-responders.

Design: Post-hoc analysis of a large randomized controlled trial.

Participants: Untreated patients with open-angle glaucoma (OAG) undergoing repeated lasers during 3-year follow-up.

Methods: Eyes failing to reach target IOP under repeated lasers were focused. The non-responder criteria were: maximum IOP reduction within 2 years after initial and repeat SLT both < 20%, and maximum IOP reduction from baseline < 25%. The comparison samples were those undergoing repeated lasers but falling the criteria. After feature selection through univariate linear models, cross-validated logistic regression models were developed using baseline and early-stage features of non-responders.

Main Outcomes Measures: Area under the receiver operating characteristic curves (AUROC) of predictive models.

Results: A total of 170 untreated OAG eyes of 98 patients were included, in which 18 eyes of 12 patients were defined as non-responders to SLT. Non-responding patients presented older age (difference, 10.0 years; 95%CI, 1.6 to 18.3 years; P=0.03) and higher proportion of females (difference, 42.4%; 95%CI, 18.9% to 45.9%; P=0.01) than responders, and non-responding eyes presented lower baseline IOP (difference, -3.6mmHg; 95%CI, -5.8 to -1.4 mmHg; P=0.001). The mean (standard deviation, SD) IOP reduction at 2 months after initial and repeat SLT was 5.6 (6.9) % and 2.2 (9.7) % in non-responders. They suffered higher risk of visual field (VF) loss progression (hazard ratio, 4.5; 95%CI, 1.2 to 16.2; P=0.02) and required more additional treatment after repeated lasers (hazard ratio, 8.9; 95%CI, 4.9 to 16.5; P<0.001) than responders during 3-year follow-up. A developed predictive model using only baseline features achieved mean (SD) AUROC of 0.84 (0.08) in cross-validation, and the model adding IOP reduction at 2 months after initial SLT achieved 0.91 (0.06). The best macro F1 score was 0.77 (0.09). Models detected non-responders through more females, older age, lower pretreatment IOP, thicker CCT, and larger IOP reduction at 2 months.

Conclusions: Non-responders to SLT needed extra attention for their uncontrolled IOP and high risk of VF progression. We developed validated machine-learning models using their presented features to achieve early detection.

Introduction

Glaucoma ranks first in the cause of irreversible blindness worldwide.[1] In open-angle glaucoma (OAG), the most prevalent subtype, selective laser trabeculoplasty (SLT) is gradually recognized as the first choice of intervention.[2–4] Although SLT has been demonstrated with superior efficacy[5,6] and cost-effectiveness[7,8] than topical intraocular pressure (IOP) lowering medicines, trade-offs between SLT and eye drops are still in dispute. In one of the controversial aspects, SLT may not yield successful results in some OAG eyes.

Previous studies have pointed out that certain features are related to the IOP reduction achieved by SLT in OAG.[9–13] A 20% reduction from pre-treatment IOP is a widely accepted criterion on SLT success, while some researchers may require greater reduction for severer eyes. A 74% of 3-year response rate of initial SLT in untreated OAG eyes was reported by Laser in Glaucoma and Ocular Hypertension Trial (LiGHT).[7] Repeat SLT was demonstrated to maintain IOP further irrespective of initial response.[14] However, some eyes could hardly reach the target level even if repeated lasers were given.[15,16] These potential non-responders to SLT needed in-depth investigation, and early detection can contribute to a more precise and personalized intervention decision in OAG.

To delve into this issue, we analyzed high-quality data from the LiGHT China trial[17] and applied interpretable machine-learning techniques to develop predictive models. We aim to figure out what features imply a possible non-responder to SLT and when ophthalmologists can pay more attention to the treatment choice in certain patients.

Methods

This study adhered to the tenets of the Declaration of Helsinki. It's a post-hoc sub-analysis of the LiGHT China trial (ChiCTR-IOR-15005924). The trial obtained ethnical approval (2014MEKY054) from Zhongshan Ophthalmic Center Ethics Committee.

Participants

Untreated OAG and ocular hypertension eyes were recruited, followed by randomization into Laser-1st Arm or Medicine-1st Arm.[17] All participants provided written informed consent for voluntary participation. Treatment escalation was performed when IOP exceeded targets or progression presented in visual field (VF) and/or disc rim following predefined guideline-based criteria (see Key Protocol in Supplement). Initial and repeat SLT were the predefined treatments in Laser-1st Arm. This study included 170 OAG eyes of 98 patients undergoing repeated lasers from 10th March 2015 to 25th April 2023.

Non-responders

In this study, OAG eyes failing to reach target IOP under repeated lasers were focused. A non-responder to SLT was defined if the maximum IOP reduction within 2 years separately after initial and repeat SLT did not reach 20%, together with the lowest IOP during follow-up did not drop over 25% from baseline. The comparison group consisted of OAG eyes which received repeated lasers but did not meet the non-responder criteria.

Model Development

Univariate linear models were used in feature selection. Features were standardized in preprocessing. Logistic regression (LR) was the backbone of our early detection models. Bayesian search was taken to optimize hyperparameters. A 5-times 3-fold repeated stratified cross-validation was applied. Metrics including area under the receiver operating characteristic curves (AUROC), precision (positive predictive value), recall (sensitivity) and F1 score (unweighted harmonic mean of recall and precision) were assessed, with a default cutoff of 0.5 predictive confidence. Model training and validation was conducted on the scikit-learn platform.[18]

Statistics

The unit of the analysis was the eye. Mixed models were used to adjust repeated measurements. Fisher exact test was applied for categorical variables and Kruskal-

Wallis test was applied for continuous variables because the samples were relatively small and non-normal. Cox regression was applied to assess the risk of certain outcomes. Statistical analysis was performed using Scipy, Statsmodels and lifelines packages based on Python.

Results

Background Characteristics

A total of 170 untreated OAG eyes of 98 patients were included in analysis, in which 18 eyes of 12 patients were defined as non-responders. Only bilateral eyes of 2 patients were allocated to different clusters. The mean (standard deviation, SD) age of non-responding patients was 55.1 (12.9) years at baseline, larger than 45.1 (13.8) years in responders (difference, 10.0 years; 95%CI, 1.6 to 18.3 years; P=0.03). Non-responders consisted of 10 (83.3%) females, higher in proportion than 36 (40.9%) females in responders (difference, 42.4%; 95%CI, 18.9% to 45.9%; P=0.01). The mean (SD) baseline IOP of non-responding eyes was 16.83 (3.00) mmHg, lower than 20.43 (4.68) mmHg in responders (difference, -3.6mmHg; 95%CI, -5.8 to -1.4 mmHg; P=0.001). Other characteristics were similar between the 2 clusters (see Table 1).

Response to Selective Laser Trabeculoplasty

The mean (SD) IOP at 2 months after initial SLT in non-responding eyes was 15.4 (2.3) mmHg, similar to 15.8 (3.9) mmHg in responders (difference, -0.4mmHg; 95%CI, -2.4 to 1.5 mmHg; P=0.84). The IOP reduction at 2 months was 5.6 (6.9) % in non-responders, inferior to 21.6 (14.8) % in responders (difference, -16.0%; 95%CI, -23.4% to -8.6%; P<0.001). The maximum IOP reduction within 2 years was 10.2 (4.8) % in non-responders, inferior to 29.2 (12.8) % in responders (difference, -18.9%; 95%CI, -25.0% to -12.9%; P<0.001). The total power of initial SLT was 50.4 (12.4) mJ in non-responders, similar to 51.7 (11.8) mJ in responders (difference, -1.3mJ; 95%CI, -7.1 to 4.6 mJ; P=0.62).

The mean (SD) IOP before repeat SLT was 16.7 (3.3) mmHg in non-responding eyes,

compared to 18.7 (4.1) mmHg in responders (difference, -2.0mmHg; 95%CI, -4.0 to 0.0 mmHg; P=0.04). The IOP at 2 months after repeat SLT was 16.4 (2.7) mmHg and 15.5 (3.4) mmHg in non-responders and responders, respectively (difference, 0.9 mmHg; 95%CI, -0.9 to 2.8 mmHg; P=0.29). Non-responders presented worse IOP reduction at 2 months (difference, -22.3%; 95%CI, -29.6% to -14.9%; P<0.001) and maximum IOP reduction within 2 years (difference, -12.2%; 95%CI, -19.4% to -4.9%; P<0.001) after repeat SLT than responders. The mean (SD) total power of repeat SLT was 62.7 (17.6) mJ and 56.5 (13.8) mJ in non-responders and responders, respectively (difference, 6.2mJ; 95%CI, -0.8 to 13.2 mJ; P=0.17).

A subset of 17 eyes with baseline IOP < 21mmHg of female responders with baseline age > 45years was selected to better illustrate the divergence. The mean (SD) age was 60.8 (9.8) years and IOP was 15.9 (2.4) mmHg. However, the subgroup CCT was 512.8 (27.4) μm, thinner than non-responding eyes (difference, -35.3μm; 95%CI, -60.1 to -10.5 μm; P=0.008). This subset achieved maximum IOP reduction of 18.0 (10.0) % and 25.9 (10.0) % using total power of 54.2 (15.7) mJ and 54.3 (15.1) mJ for initial and repeat SLT, respectively.

Non-responders suffered higher risk of VF loss progression than responders (hazard ratio, 4.5; 95%CI, 1.2 to 16.2; P=0.02), illustrated in Figure 1. They required additional treatment after repeated lasers more than responders (hazard ratio, 8.9; 95%CI, 4.9 to 16.5; P<0.001). A total of 14 eyes received topical IOP-lowering medicines after repeated lasers. Taking the maximum IOP reduction within 2 years after first medicine prescription as an anchor, the mean (SD) IOP was 12.9 (1.7) mmHg, with reduction of 22.4 (7.0) % from baseline. The number of medicines used was 1.5 (0.8) types (see Table 2).

Model Performance for Early Detection

Differentiating baseline features including age, gender, IOP and CCT were chosen for model development. The IOP reduction at 2 months after initial SLT was also applied.

These features and related models were named by data source like ‘baseline’ (BS) and ‘follow-up’ (FP) in the following outcomes.

Model BS used only baseline features and achieved mean (SD) AUROC of 0.84 (0.08), similar to 0.88 (0.04) of model FP which used only follow-up data (difference, -0.03; 95%CI, -0.07 to 0.01; P=0.27). Model BS+FP achieved AUROC of 0.91 (0.06) and F1 macro of 0.77 (0.09) by combining all data. The cross-validation ROC curves were presented in Figure 2. The F1 on detecting non-responders was improved from 0.46 (0.10) to 0.60 (0.15), compared to Model FP (difference, 0.08; 95%CI, 0.02 to 0.13; P=0.01). Improvements were also seen in precision (difference, 0.11; 95%CI, 0.02 to 0.19; P=0.03) and recall (difference, 0.18; 95%CI, 0.04 to 0.32; P=0.05) in Model BS+FP (see Table 3).

Models detected non-responders through more females, older age, lower pretreatment IOP, thicker CCT, and larger IOP reduction at 2 months (see eTable 4 in Supplement).

Discussion

Recently, SLT has been recommended as the first choice in the treatment of OAG.[2–4] However, previous studies noticed that the IOP of some OAG eyes were unable to be effectively lowered by SLT.[7,10] In-depth investigation into the non-responders is important for further clinical application and promotion of SLT. This study revealed that female, older age, lower IOP and thicker CCT were risk factors of poor response to SLT. Non-responders suffered higher risk of VF progression than responders and most of them needed additional topical IOP-lowering medicines after repeated lasers. This study also developed validated machine-learning models to achieve early detection of the non-responders to SLT, which can contribute to precise and personalized clinical decision-making.

Eyes failing to reach target IOP under repeated lasers were focused here, because most OAG eyes can reach IOP control effectively and safely by repeated lasers even if the

initial response was not satisfying. Previous studies have investigated the predictive factors of a single SLT success. Commonly, the IOP-lowering effect was the main focus and a 20% reduction from pre-treatment IOP was used as a success criterion.[11,19–21] The LiGHT China trial followed a "Treat in Pursuit of Control" design,[17,22] and thus, defined target IOP based on severity clusters[23,24] and concerned glaucoma progression in the assessment of SLT success. Failure presented when our treatment escalation criteria were triggered and subsequent intervention was added. Thus, the non-responders to SLT were defined by the maximum IOP reduction with 2 years after SLT < 20% and the lowest IOP during the whole 3-year follow-up <25%, who were probably "uncontrolled" under repeated lasers. The potential to respond to SLT was reflected better by maximum reduction than reduction at a time-mark.

Our considerations had been confirmed. The defined non-responding eyes got only 5.6% and 2.2% mean IOP reduction at 2 months after initial and repeat SLT, while responders achieved 21.6% and 24.5%. Even though we turned to the maximum IOP reduction within 2 years, they were only 10.2% and 10.6% on average in non-responders. Thus, these non-responding eyes suffered 4-time higher risk of VF loss progression in 3 years and most of them needed additional topical medicines to better control their IOP.

Interestingly, the non-responders and responders had similar IOP after SLT. Many of the previous studies pointed out that pretreatment IOP was a strong predictor of the IOP-lowering effect of SLT.[9,19,25,26] These phenomena implied the appropriate pretreatment IOP for SLT and the post-laser IOP to anticipate. It can be validated by another subset of responders with similar baseline features to non-responders in this study. Although they were recorded with low pretreatment IOP close to non-responders, their CCT was relatively thinner so their corrected IOP should be higher than observed values,[27] which partly explained why they responded to SLT better.

Female and older age were the other two distinctive baseline features spotted in non-responders. Previous studies also concerned whether these two demographic features

were related to SLT success. However, there were lots of disputes. Some reported uncorrelation,[12,20] while others reported older age was related to greater SLT success rate.[19] Recently, the LiGHT trial reported that female (coefficient, -1.42; 95%CI, -2.29 to -0.54; P=0.002) and age (coefficient, -0.04; 95%CI, -0.08 to 0.00; P=0.05) was negative correlated with the IOP-lowering effect of SLT.[7] Existing disputes on the contribution of SLT outcomes from gender and age were possibly because of the relatively weak relationship. LiGHT provided a piece of high-quality evidence on this aspect with its design and large sample size.

It should be emphasized that although we found certain features related to poor response to SLT, it didn't mean that an OAG eye doomed to be non-responding with these features. Many other factors can influence the SLT effect and the underlying mechanism has yet to be clarified. An important example is trabecular pigments. Larger IOP reduction from SLT was theoretically related to greater trabecular pigments, but existing evidence did not support any correlation,[11,20,28] partly because the assessment of trabecular pigments depended on subjective views. In this study, we noticed some eyes with risk factors still responded well to SLT. Thus, it's a multifactorial outcome, and we aimed to find useful clues to enhance clinical decision-making.

Early detection of the non-responders to SLT is necessary. For patients, persistent uncontrolled IOP led to higher risk of VF loss progression, which can cause irreversible imparity on quality of vision and life.[1,29] For ophthalmologists, choosing appropriate intervention is essential in the long-term management of glaucoma. We developed validated models to detect potential non-responders at baseline and at early stage after SLT.

The IOP reduction at 2 months provided valuable information about the response outcomes. In our protocol, the 2-month mark was the first scheduled observation point and treatment escalation wasn't allowed until 2 months. The model based on the IOP reduction at 2 months achieved an AUROC of 0.88 on average. However, the model

based on the differentiating baseline features achieved similar performance in every aspect, and achieved earlier detection before treatment. Further, model using combined data achieved an AUROC of 0.91 and massively improved the precision, recall and F1 score in detecting non-responders. This model with the best performance was able to recognize most of non-responders (0.75 on average) with relatively ordinary precision (0.50 on average). It was consistent with what we illustrated earlier: non-responders presented certain features, but patients with these features might be responders.

Our predictive models were validated through repeated cross-validation, and they showed excellent robustness and interpretability. These models provided chance before and after SLT for ophthalmologists to assess whether their OAG patients needed extra attention. Although these models were trained on newly diagnosed medicine-naïve patients, they were possibly able to be applied on patients using medicines because some studies reported that pretreatment IOP was the important predictor and medicines seemed to have no significant influence on SLT effect.[20,28]

This study had certain limitations. First, external validation has yet to perform. Although cross-validation is strict and convincing, external validation plays important role in further assessing the generalization ability of models in different contexts. Additionally, the sample size was relatively small, because our focus was non-responders under repeated lasers. Evidence on a larger sample is expected in the future.

In conclusion, we demonstrated that female, older age, lower IOP and thicker CCT were risk factors of the non-responders to SLT. Non-responders needed extra attention because they were unable to control IOP through SLT and suffered higher risk of VF progression than responders. We developed validated models to achieve detection of non-responders at baseline and at early stage after SLT, potentially improving the clinical decision-making of OAG treatment.

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Figure Legend

Figure 1 Cox Regression Curves for VF Loss Progression

Survival curves of non-responding and responding eyes free from VF loss progression, estimated by cox regression. Non-responders suffered higher risk of VF loss progression than responders in the 3-year follow-up. The mean (95%CI) hazard ratio was 4.5 (1.2 to 16.2).

CI = confidence interval; VF = visual field.

Figure 2 Cross-validation ROC curves of Model BS+FP

All ROC curves of the 3-fold 5-time cross-validation were plotted in translucent colorful lines. The solid blue curve represented the mean ROC, and the grey region represented 1 SD from mean. The mean (SD) AUROC of model BS+FP was 0.91 (0.06).

AUROC = area under ROC curve; BS = baseline; FP = follow-up; ROC = receiver operating characteristic curve; SD = standard deviation.