HIOP-Reader: Automated Data Extraction for the Analysis of Manually Recorded Nycthemeral IOPs and Glaucoma Progression

Running Title: Automated 24h IOP Analysis and Glaucoma

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Précis: Nycthemeral intraocular pressure (IOP) monitoring is commonly used in Europe to detect glaucomatous IOP values. Using efficient, machine learning data extraction tools to study manually drawn IOP charts, we found no correlation between any IOP parameters and glaucoma progression.

Keywords:

glaucoma progression; nycthemeral intraocular pressure; mean ocular perfusion pressure

Abstract

Purpose: Nycthemeral (24-hour) glaucoma inpatient intraocular pressure (IOP) monitoring has been used in Europe for more than 100 years to detect peaks missed during regular office hours. Data supporting this practice is lacking, partially because it is difficult to correlate manually drawn IOP curves to objective glaucoma progression. To address this, we deployed automated IOP data extraction tools and tested for a correlation to a progressive retinal nerve fiber layer loss on spectral-domain optical coherence tomography (SDOCT).

Methods: We created a machine learning image analysis software to extract IOP data from hand-drawn, nycthemeral IOP curves of 225 retrospectively identified glaucoma patients. The relationship between demographic parameters, IOP and mean ocular perfusion pressure (MOPP) data to SDOCT data was analyzed. Sensitivities and specificities for the historical cutoff values of 15 mmHg and 22 mmHg in detecting glaucoma progression were calculated.

Results: IOP data could be extracted efficiently. The IOP average was 15.2±4.0 mmHg, nycthemeral IOP variation was 6.9±4.2 mmHg, and MOPP was 59.1±8.9 mmHg. Peak IOP occurred at 10 AM and trough at 9 PM. Disease progression occurred mainly in the temporal-superior and -inferior SDOCT sectors. No correlation could be established between demographic, IOP, or MOPP parameters and SDOCT disease progression. The sensitivity and specificity of both cutoff points (15 and 22 mmHg) were insufficient to be clinically useful. Outpatient IOPs were non-inferior to nycthemeral IOPs.

Conclusion: IOP data obtained during a single visit make for a poor diagnostic tool, no matter whether obtained using nycthemeral measurements or during outpatient hours.

Introduction

The need for better diagnostic options in glaucoma is critical, as this disease only presents symptoms at an advanced stage and is often diagnosed late.[1] 42% of all primary open angle glaucoma (POAG) patients ultimately go blind in one eye,[2] partially because of this. To better assess the effectiveness of the treatment and to detect pressure peaks that are not recognized during office hours,[3] patients in German-speaking countries are often admitted for nycthemeral (24-hour) intraocular pressure (IOP) profiles.[4] Such monitoring generates costs averaging EUR 643 per night[5,6] and has been obtained, based on verbally communicated past use patterns at many clinics, at least approximately one million times in the last 100 years[4,7–9] to aid in the diagnosis and treatment of glaucoma. However, evidence supporting 24-hour IOP profiles for identifying IOPs above target or larger than normal IOP fluctuations[4,8–11] is at most expert opinion (level V).[12–14] The absence of strong evidence for 24-hour IOP profiles as a diagnostic tool in glaucoma is surprising, considering the contrast to the high-quality level I evidence that establishes IOP as the preeminent cause of glaucoma.[12–14] Damage from high IOP is an experimentally demonstrated pathomechanism of glaucoma in nonhuman primates.[15,16] Elevated IOP levels are strongly correlated to human glaucoma incidence,[17,18] and their treatment reduces glaucoma onset and progression.[19,20] Moreover, IOP fluctuations and pressure peaks during outpatient clinic hours have previously been associated with glaucoma progression.[21]

One reason for the missing link between vast historical records of 24-hour IOP profiles and glaucoma progression may be the difficulty in extracting data from manually drawn IOP curves that are paper-based and correlating them to objective, statistically significant progression. To address this, we created a computer-aided image analysis of 24-hour IOP profiles. We matched them to worsening retinal nerve fiber layer thickness using current spectral domain optical coherence tomography and software (SPECTRALIS SDOCT, Heidelberg Engineering, Heidelberg, Germany). Similarly, we estimated the ocular perfusion pressure and determined the strength of correlation to progression.

High IOP damages the axons of retinal ganglion cells primarily at the level of the lamina cribrosa, a biomechanical weak point.[22,23] Too low an ocular perfusion pressure[24] is considered to be a secondary contributing factor. Based on this, our primary hypothesis was that 24-hour inpatient IOPs are correlated to a statistically significant decline of the retinal nerve fiber layer (RNFL), in particular the temporal-superior, temporal or temporal-inferior RNFL. Our secondary hypothesis was that ocular perfusion pressure is correlated to glaucoma progression.

Methods

Study design

This retrospective chart review was carried out at the Department of Ophthalmology of the University of Würzburg. It abided by the principles stated in the declaration of Helsinki. Due to its retrospective nature, informed consent was waived by the Institutional Review Board of the University of Würzburg. Charts of 225 patients admitted to the ophthalmology inpatient unit at the University Hospital of Würzburg for nycthemeral IOP monitoring from 2017 to 2019 were analyzed to comprise two years since the introduction of OCT-aided progression analysis in this hospital. Only right eyes were analyzed to reduce bias. Patients included had a diagnosis of primary open angle glaucoma (POAG), low-tension glaucoma (LTG), pseudoexfoliation glaucoma (PXG), pigmentary glaucoma (PG), and juvenile glaucoma (JOAG). Patients with terminal, neovascular, uveitic, or angle-closure glaucoma were excluded from the study. Terminal glaucoma was defined as having a nearly complete visual field loss or a cup-to-disc ratio of 1.0.

Parameters recorded included age, gender, diagnosis, history of surgery, family history of glaucoma, medications, slit lamp, fundoscopic examination findings, and the central corneal thickness. The 24-hour IOP protocol established in this hospital called for measurements in the habitual position with 10 AM, 2 PM, 5 PM, and 9 PM readings obtained by Goldmann applanation tonometry (Haag-Streit, Köniz, Switzerland) in the sitting position, and the 12 AM measurement obtained by Perkins applanation tonometry (Perkins MK3, Haag-Streit, Köniz, Switzerland) in the supine position. IOPs were recorded on paper charts using blue for right eyes and red for left eyes **(Fig. 1)**. Each subject's 24-hour IOP data was fit to a cosine curve. Because there were only five measurements, instead of at least twelve, this fit was done manually using a sparkline macro [3,25]. The acrophase was estimated by defining it as the phase timing, in which a peak IOP during the 24 hours was reached. Paper-based 24-hour IOP profiles were examined using a custom-made computer-aided image analysis program. Values noted were: T_{max}, T_{min}, T_{avg}, and IOP_{var} (T_{max} - T_{min}). Additionally, the mean ocular perfusion pressure (MOPP) was calculated as two-thirds of the difference between the mean arterial pressure and T_{avg}.

Image analysis of manually recorded 24-hour IOP profiles

We wrote the Python-based program *HIOP-Reader* [26] to extract patient name, examination date, and the IOP values on the y-axis with their corresponding time on the x-axis. We used OpenCV [27] for image processing, Tesseract [28] for optical character recognition, and TensorFlow [29] and scikit-learn [30] for machine learning. The image analysis was divided into three parts: preprocessing, value detection, and name and date extraction.

The main goal of preprocessing was to detect the frame containing the IOP profile and crop the image to it. We achieved this by searching for curves, joining all continuous points with the same intensities. In OpenCV, this is referred to as contours. To improve the accuracy of finding contours, we binarized the image by applying adaptive thresholding. We used Gaussian adaptive thresholding, which calculates the Gaussian weighted sum over a neighborhood of, in our case, 27x27 pixels, to find an appropriate threshold value. This threshold, minus a constant C=10, was then used to binarize the image. From the binary image, we chose the largest resulting contour as the main frame of the image. To make the process more robust, we ensured that the resulting contour is a rectangle. This was done by approximating the contour using the Douglas-Peucker algorithm,[31,32] ensuring that the contour consisted of four lines even when the frame was cutoff or other artifacts were obstructing the frame. Next, we checked the angles between the four lines of the approximated contour, ensuring that it was at least close to a rectangle. Finally, we cropped the image to the resulting approximation of the largest contour, resulting in an image cropped to the main frame of the IOP profile. After cropping, all scanned images had the same format and size, enabling us to do precise pixel position-based operations.

To extract the IOP values entered into the profile, we detected the lines representing the different examination times using the Canny edge detection algorithm[33] and Hough line transformation.[34] Any falsely detected or horizontal lines were removed. This left us with the precise positions of the lines representing different times. For each line, a neighborhood around it was considered when searching for IOP values. We exploited the fact that all IOP values for the left eye were entered in red, while all values for the right eye were entered in blue and created color-specific masks. These masks only contained the part of the image that was blue or red, respectively. IOP values were collected using these masks and the immediate vicinity of each line. Lastly, since all images had the same format, the IOP value could be directly inferred from the pixel position of the detected entry.

To capture the date of the 24-hour IOP profile, we applied a traditional machine learning approach. First, we isolated the area where the date was recorded and separated the numbers and the delimiters using contours. The numbers were then predicted using a convolutional neural network trained on the Modified National Institute of Standards and Technology (MNIST) dataset.[35] As the patient names were mostly recorded using machine-written labels, optical character recognition with Tesseract[28] could be used to extract all machine-written text on the form. We used regular expressions on the extracted text to find patient names. All information was manually confirmed and stored as CSV files. To allow for rapid editing and error correction, we developed a graphical user interface for the program.

Statistical Analysis

Data Management

Confirmatory and exploratory data analysis was performed using JMP (JMP 15.2.1, SAS Institute Inc., Cary, North Carolina, USA). Means along with standard deviations were calculated for continuous variables, while percentages were computed for categorical variables. A Kolmogorov-Smirnov test was run to assess continuous variables for a normal distribution. Bivariate analysis was used to study the relationship between various IOP parameters. Independent sample t-tests were used to compare means of continuous variables, whereas a chi-square test compared those of categorical variables. Spearman's rank-order correlation coefficient (rather than a Pearson's correlation coefficient) was reported if data sets were not normally distributed. For all our analyses, a p-value of 0.05 or less was considered statistically significant.

OCT & Disease Progression Analysis

Disease progression was assessed using a spectral domain OCT (SPECTRALIS OCT, Heidelberg Engineering GmbH, Heidelberg, Germany). The retinal nerve fiber layer (RNFL) thickness (in micrometers) of all peripapillary sectors was recorded. Changes in RNFL thickness were evaluated using commercial software (HEYEX Version 2.4.1., Heidelberg Engineering GmbH, Heidelberg, Germany), which provided both the rate of RNFL loss and a statistical comparison to a normal age-related RNFL loss rate. In this way, progression was calculated both as a continuous and a dichotomous variable. Linear regression was utilized to assess the relationship between several continuous variables (such as IOP_{var}) and the rate of RNFL loss, representing disease progression. A contingency analysis was carried out to determine the sensitivity and specificity of using 15 and 22 mmHg as T_{max} cutoff points in detecting disease progression in any sector. These sensitivity and specificity measurements were then calculated with 10 AM, 2 PM, and 5 PM values to compare these values to a hypothetical outpatient situation.

Results

Table 1 depicts the demographic variables of the 225 patients included in this analysis. Five eyes were excluded due to meeting our criteria for terminal glaucoma. There were 137 women (61%) and 88 men (39%). Women were significantly older than men (77.0±10.0 years versus 72.8±12.6 years, respectively, p=0.006). The diagnoses included were POAG (n=130, 57.8%), LTG (n=41, 18.2%), PXG (n=39, 17.3%), GS (n=8, 3.6%), PG (n=4, 1.8%), and JOAG (n=3, 1.3%). Patients with POAG, LTG, and PXG were older than those with PG and JOAG (p < 0.001) **(Fig. 2)**. Compared to the 3:2 ratio of women to men in this study, there were disproportionately more women (78%, n=32) with LTG than men (22%, n=9). There was no statistically significant difference in the number of medications per eye in both groups, with an average of 2.2 drops in each group (p=1.0, **Table 1**). Fifty-eight patients had four different topical glaucoma medications, with prostaglandin analogs being the most prescribed medication (31.6%), followed by carbonic anhydrase inhibitors (27.0%), alpha agonists (22.0%), and beta-blockers (19.4%). The mean central corneal thickness (CCT) was 526.3±35.7 µm. There was no gender difference (females: 538.6 ±34.0 µm, males: 534.8 38.3 µm, respectively, p=0.43).

We evaluated HIOP-Reader on 100 IOP profiles. An average of 3.60±0.81 seconds was needed to process a file, not accounting for human error correction. In contrast, manual data extraction took 429.06±96.61 seconds or 119 times longer. The IOP curves showed a mean of 8.43 entries per eye. The names were detected correctly with an accuracy of 75.32%, the detection of the date was only accurate in 42.85% of the cases. The entered values were detected with high accuracy. On average, there were 0.4675 falsely detected entries per IOP curve. Given the average of 8.43 entries per eye, this results in a false-positive rate of 5.54%. An average of 0.3376 entries per IOP curve were not detected, resulting in a false-negative rate of 4%. For the detected entries, the average distance between the actual value and the predicted value was 0.0927. We observed a mean value of 14.72 per entry, giving us a mean relative error of 0.63%. The evaluation was performed on standard consumer hardware from 2019 with a 2,4 GHz Quad-Core Intel Core i5-8279U CPU and 16 GB of random access memory. LTG had a significantly lower T_{avg} and T_{max} than POAG and PXG (p=0.005 and p<0.001, respectively; **Fig. 3**). The CCT of LTG was not significantly different from POAG or PXG (both p>0.05). IOP_{var} was correlated with T_{max} (correlation 0.8, p<0.001) and with T_{avg} (correlation 0.3, p<0.001) but not with T_{min}.

The observed average IOPs were relatively similar throughout the day and ranged from a peak of 15.8±5.1 mmHg at 10:00 to a trough of 14.5±4.6 mmHg at 21:00 (p=0.519; **Fig. 4**). One hundred-nine patients had an acrophase with peak IOP at 10:00 AM. The acrophase spread was 8.4±3.8 hours. When all 24-hour IOP curves were adjusted to have matching acrophases, a peak IOP of 18.1±5.3 mmHg was reached at 10:00 AM and a trough of 14.2±4.1 mmHg at 21:00 ($p<0.001$; **Fig. 5**).

OCT progression data were available in 116 out of 225 patients. Of those, 42% were progressors with a significantly worsening retinal nerve fiber layer thickness. More patients had progression in the TI (31%) and TS (36%) sector than in T (22%). Most progressions occurred in the TS and TI sectors (**Fig. 6**). Between progressors and non-progressors, there were no differences in age, gender, or type of glaucoma, nor was there a difference in their IOP peak time, IOP_{var}, T_{max}, T_{avg}, or T_{min} (all $p>0.05$). IOP_{var} was 6.3±3.6 mmHg in progressors and 6.8±3.9 mmHg in non-progressors, respectively. There was no difference in age. The RNFL decline in these progressors had an average of 2.3±1.7 microns per year. Applying an old concept that IOP variations of more than 5 mmHg may indicate glaucoma progression underlying the rationale of obtaining inpatient, 24-hour IOP measurements[4], sensitivity for such variation to detect glaucoma progression was 68% and specificity 25%.

Applying a historical cutoff of 22 mmHg as an IOP considered too high, sensitivity was only 7%, and specificity was 87%. When a cutoff of 15 mmHg was chosen, corresponding to a normal IOP of healthy eyes often viewed as suboptimal for moderate to advanced glaucoma, sensitivity was 69%, and specificity was 23%. **Table 2** shows the sensitivity and specificity of those cutoff values obtained during 24-hour measurements and compares them to the same IOP criteria if those were applied to regular outpatient clinic hours. The specificity of the criteria "15 mmHg" during outpatient hours was slightly better than when applied to inpatient 24-hour measurements, while the criteria "22 mmHg" were very similar. **Figure 7** applies the concept of Tmax and Tavg as a test for glaucoma progression to a receiver operating characteristic (ROC) curve. All curves, regardless of inpatient or outpatient values, were close to the reference line, indicating poor performance.

Table 3 summarizes the correlations we found. T_{max}, T_{avg}, T_{min}, and IOP_{var} were not correlated to the slope (speed) of RNFL loss ($p > 0.05$). These parameters were also not correlated to structural differences between the expected, normative RNFL thickness or the actual (absolute) RNFL thickness measured by the SPECTRALIS OCT.

The estimated MOPP was 59.1±8.9 mmHg. This parameter did not differ by glaucoma type ($p=0.42$) or sex ($p=0.79$). MOPP correlated negatively and weakly to the slope of the temporal-superior retinal fiber layer thickness ($r=-0.09$, $p = 0.04$), to T_{avg} ($r=-0.14$, $p=0.04$), T_{max} ($r=-0.15$, $p=0.03$) and T_{min}

(r=-0.14,p = 0.04) but not to IOP_{var} (p=0.72). There was no significant correlation between MOPP and worsening glaucoma (p=0.34). This was also not the case in LTG (p=0.14).

Discussion

We developed a high-efficiency reader specifically to extract nycthemeral IOP data from manually drawn charts and assessed disease progression using an SDOCT with progression analysis software. We found no significant relationship between nycthemeral IOP measurements and glaucoma progression, despite the best efforts.

HIOP-Reader allowed us to rapidly process and extract a large amount of image data with a low error rate. This program is made available to the scientific community via GitHub,[26,36] a public software repository. Further improvements could be made with date extraction using component labeling and support vector machine classification[37] or Hidden Markov Model[38] based methods. The functionality that allows for statistical analysis of handwritten IOP profiles worked well. In particular, the program showed resilience to imperfections inherent to IOP profiles drawn manually by different users, and the IOP values were detected with high accuracy. This allowed us to process and use large amounts of handwritten data that would have been hard to acquire. We believe HIOP-Reader will be a useful mining tool to process the many decades of data available at inpatient-based ophthalmology clinics that have performed nycthemeral IOP measurements in the past.

Regarding patient demographics in our study, the gender ratio of women (61%) to men (39%) was very similar, almost down to the digit, to that of global glaucoma studies.[39,40] Among glaucoma subtypes, LTG, in particular, is more prevalent in women,[41] a pattern seen in our study as well. Except for age, the demographic variables of men and women did not differ.

The idea behind collecting 24-hour IOPs appears to have been that glaucoma patients might have a higher nocturnal peak and a larger IOP variation than normal eyes[4,7–9,11] when in fact, it has been known for a while that healthy eyes have a larger IOP variation than glaucomatous eyes.[42] Looking for nocturnal peaks may also be of limited diagnostic value, as an elevated nocturnal IOP in the supine position is a physiological reaction in healthy and glaucomatous eyes.[42] Research into the relationship between IOP variation and glaucoma progression has produced discordant findings, however.[43–47] A study of 105 POAG eyes with normal in-office IOP values showed IOP ranges over five days to be an independent risk factor for disease progression (defined as visual field loss).[43] Similarly, some studies showed short-term (48-hour) and long-term IOP fluctuations to be correlated to visual field progression.[44,47,48] Other investigators failed to corroborate these factors.[45,46] One reason for this may be the inclusion of glaucoma patients undergoing medical therapy, who have a smaller fluctuation range.[49] A 2007 study on 71 treated POAG eyes compared office IOP (9 AM - 6 PM) to 24-hour IOP readings and showed no statistical significance in the mean IOPs of both groups.[50] In another study, the office IOP fluctuation was substantially lower than that of 24-hour measurements, and the two were not be correlated.[50] Interestingly, a different study found that the mean outpatient IOP could, in fact, be used to predict both mean and peak nycthemeral IOPs.[51]

We found nycthemeral and office IOP variables to have an inadequate sensitivity and specificity in identifying progressors, as the ROC curves demonstrate. Well-performing medical diagnostic tests, such as the SDOCT, have a value close to 90% in both parameters (resulting in a hyperbolic curve shape).[52] This does not mean that there is no connection between 24-hour IOP variables and glaucoma progression. Instead, our findings highlight the challenges of implementing a well-intended test in a busy clinical environment without the proper methods. New evidence has emerged demonstrating that IOP peaks and variation in 24-hour IOP measurements are indeed linked to glaucoma pathogenesis when operator-independent, implantable IOP-sensors or contact lenses are used to record pressures at home.[53–56]

The retrospective IOP data we processed in this study had considerable shortcomings. Values were recorded with a commitment to seemingly arbitrarily set times, unevenly distributed throughout the day, and at an interval larger than the 2-hour interval of IOP sleep lab studies.[3,25] Such a customized schedule might fit clinicians' work schedules better, but it prevents finding the best fitting cosine curve and the peak (acrophase) as the phase timing of the 24-hour rhythm.[25] The IOP peak at 10 AM in our data appeared to be later than in previous studies, but this is unlikely to be the actual phase timing. Other studies reported peaks around 5:30 AM,[57] 6 AM,[58] 8 AM,[59] and troughs at 2 PM,[59] 5 PM,[44] and 9:30 PM,[57] respectively.

We found MOPP to be negatively correlated to T_{avg}, T_{max}, and T_{min}. This is not surprising, as one would expect the perfusion pressure to increase somewhat as the IOP decreases. Our MOPP did not correlate to progression, on the other hand, as suggested by other studies that examined POAG, PXG, and LTG.[19,60–62] A reduced nocturnal ocular perfusion pressure, in particular, has been associated with increased structural damage and visual field deterioration in LTG patients.[60,63] The blood pressure readings we used for the MOPP estimation were obtained on admission during late morning hours, however.

Our study points to several problems with obtaining 24-hour inpatient IOPs. First, values measured during an inpatient stay may not reflect values at home due to maximized drop compliance in a clinic environment with close observation. Second, even if they did, diurnal intraocular pressure patterns are often neither sustained nor reproducible.[64] Third, if a patient is already known to have a statistically significant decline on SDOCT, a test with high sensitivity and specificity, it is difficult to see how a nycthemeral IOP profile could be used to argue against advancing therapy. Fourth, although the Perkins tonometer used here for supine IOPs can be as accurate as Goldmann applanation tonometry,[65] it is highly operator-dependent and requires experience, not all on-call residents might have. A pneumatonometer,[66] a well-accepted standard for 24-hour IOP studies with high accuracy and reproducibility, would be a better choice.[42,67] Given these issues, it is surprising that the practice of obtaining nycthemeral IOP profiles has been continued for more than a century. Answers might perhaps be found in how this practice appears to be limited to countries that could follow the literature on that topic in German[4,7–10,68] and how these continue to favor inpatient reimbursements[69] although ophthalmology started to become an outpatient specialty in the late 1980s.[70–73]

In conclusion, we created software which acquired nycthemeral IOP data from hand-drawn IOP charts and performed at more than 100-times the speed of manual extraction. No correlation could be found between any IOP parameters or MOPP and objective glaucoma progression. ROC curves indicated a poor performance of 24-hour inpatient IOPs as a diagnostic tool.

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Tables

Table 1

Table 1: Demographics parameters of included patients.

	Males (n = 88)	Females (n = 137)	p-value	Total
age (years)	72.8 ± 12.6	77.0 ± 10.0	0.006*	75.4 ± 11.2
central corneal thickness (micrometers)	534.8 ± 38.3	538.6 ± 34.0	0.43	536.3 ± 35.7
average number of drops	2.2 ± 1.6	2.2 ± 1.5	1.00	2.2 ± 1.5
average number of surgeries	0.6 ± 0.7	0.6 ± 0.8	0.77	0.6 ± 0.7
T_{avg} (mmHg)	15.9 ± 5.0	14.7 ± 3.1	0.03	15.2 ± 4.0
T_{max} (mmHg)	20.3 ± 6.9	18.7 ± 4.0	0.03	19.3 ± 5.4
IOP_{var} (mmHg)	7.4 ± 4.9	6.6 ± 3.7	0.17	6.9 ± 4.2
MOPP (mmHg)	58.8 ± 9.0	59.3 ± 8.8	0.68	59.1 ± 8.9

Table 2

Table 2. Comparison of sensitivity and specificity between progression as nominal variable and T_{max} measurements using 15 and 22 mmHg as cutoff values.

cutoff value	parameter	24h-IOP	OP-IOP	difference
15 mmHg	sensitivity specificity	0.69 0.23	0.63 0.40	0.06 -0.17
22 mmHg	sensitivity specificity	0.07 0.87	0.06 0.89	0.01 -0.02

OP-IOP = IOP measurements during outpatient hours (10 AM, 2 PM, 5 PM).

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Table 3

Table 3. Correlation coefficients for IOP and progression

	T_{avg}	T_{max}	T_{min}	IOP_{var}	MOPP
T_{avg}	-				
T_{max}	**0.74***	-			
T_{min}	**0.87***	**0.54***	-		
IOP_{var}	0.11	**0.64***	**-0.21***	-	
MOPP	**-0.14***	**-0.15***	**-0.14***	-0.025	-
G SL	-0.09	-0.04	0.06	-0.01	-0.05
TS SL	-0.04	-0.1	-0.15	< -0.01	**-0.09***
T SL	-0.05	-0.05	0.03	-0.04	-0.04
TI SL	-0.11	-0.09	-0.01	-0.01	-0.02

Spectralis OCT parameters G SL = slope of global RNFL loss, TS SL = slope of temporal-superior RNFL loss, T SL = slope of temporal RNFL loss, TI SL = slope of temporal-inferior RNFL loss, MOPP = mean ocular perfusion pressure, * = significant at 0.05

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Figures

Figure 1

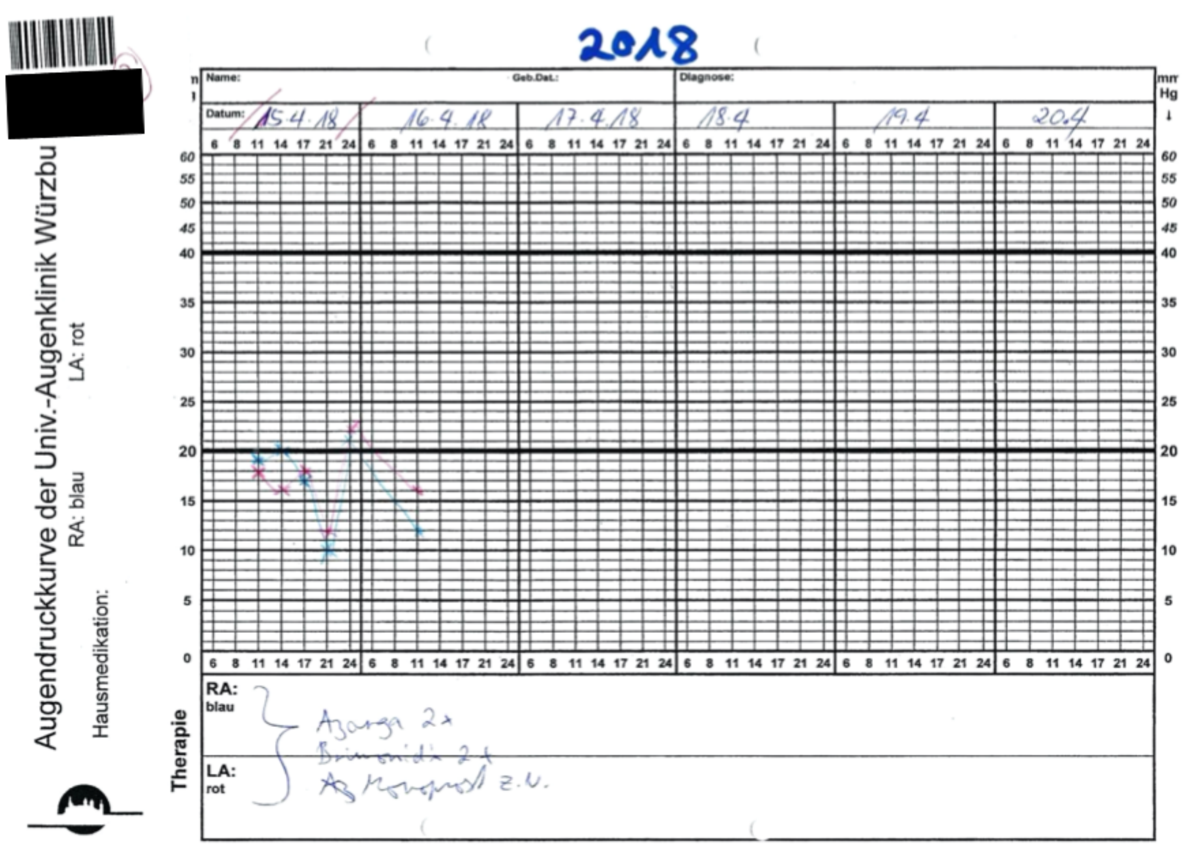
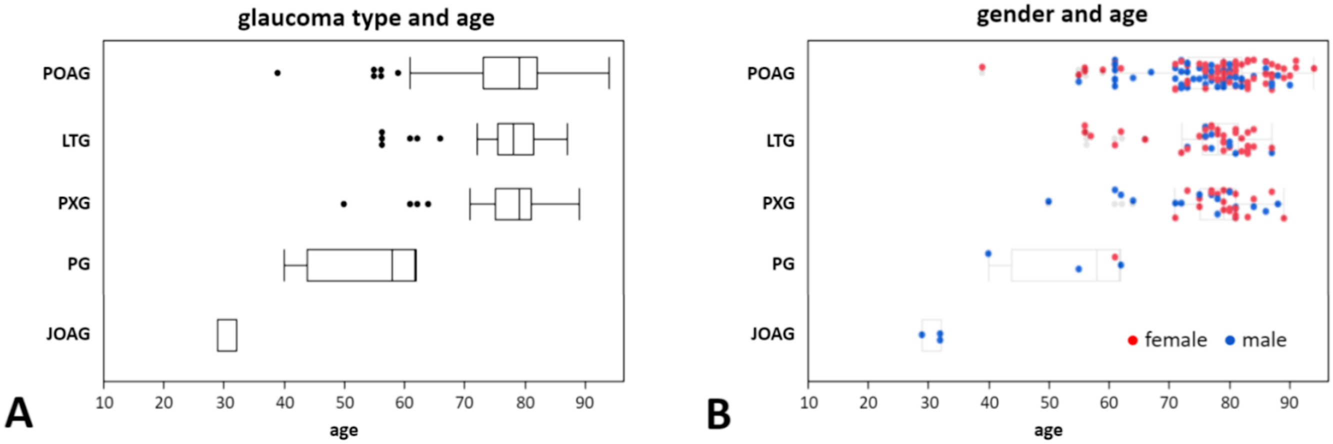


Figure 1. Example of an IOP chart used throughout the country of this study to this day. The time is displayed on a non-linear x-axis with uneven intervals and the IOP on a non-linear y-axis with a scale compressed above 40 mmHg. The length of the x-axis of this chart template indicates that IOP curves were sometimes obtained for six days. Blue= right eye, red= left eye. A patient-identifying sticker is blacked out in the left upper corner.

488 **Figure 2**

489 

490 **Figure 2:** A) Glaucoma type and age distribution. POAG, LTG, PXG, and GS patients had similar averages, while PG
491 were younger and JOAG were the youngest. B) Gender and age distribution. There were disproportionately more
492 female LTG patients who were younger than male LTG patients.

Figure 3

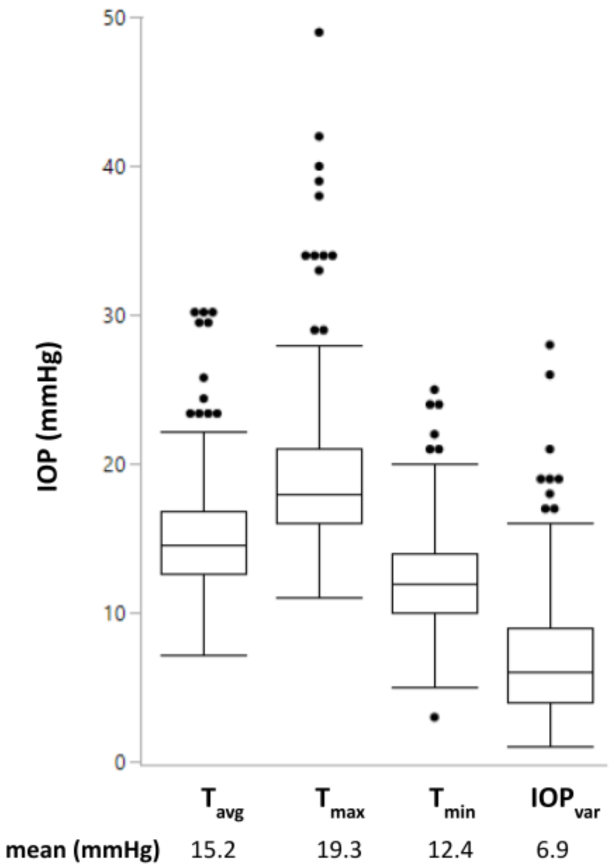


Figure 3: IOP average, maxima, minima, and variation.

Figure 4

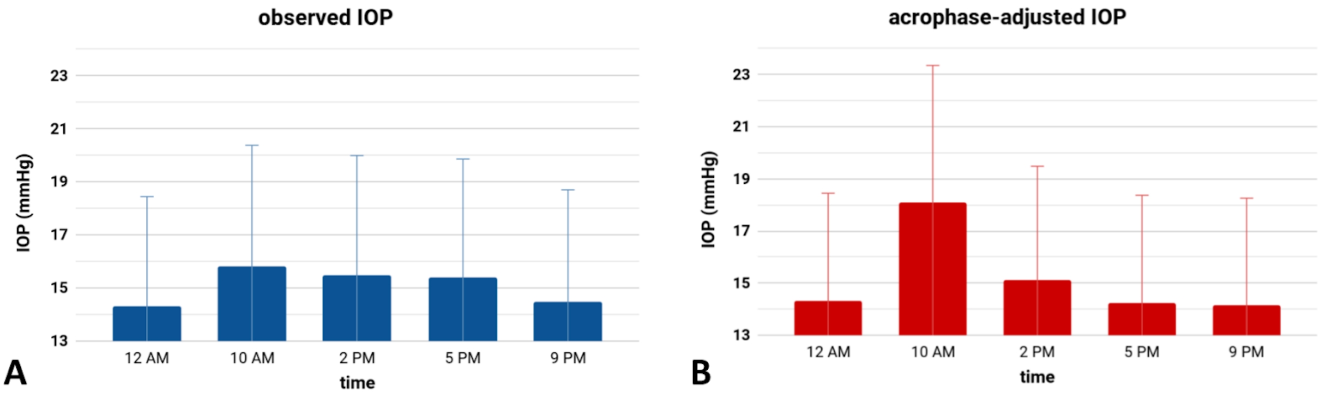


Figure 4: Nycthemeral (24-hour) IOPs as observed (A) and when arranged by estimated acrophases (B).

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Figure 5

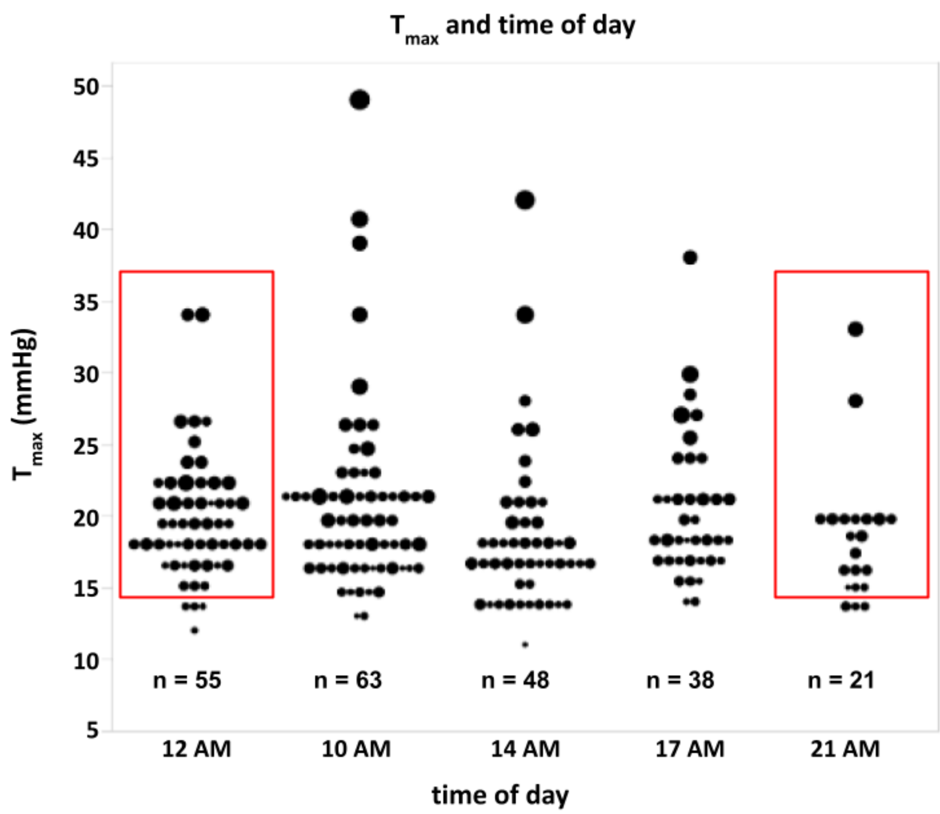

Figure 5: T_{max} and time of day at which T_{max} was reached. Each bubble represents the T_{max} of one patient during the 24h IOP inpatient measurement. The bubble size indicates the amount of 24-hour IOP variation. Red boxes indicate T_{max} measurements above 15 mmHg that would not be detected during typical outpatient office hours.

Figure 6

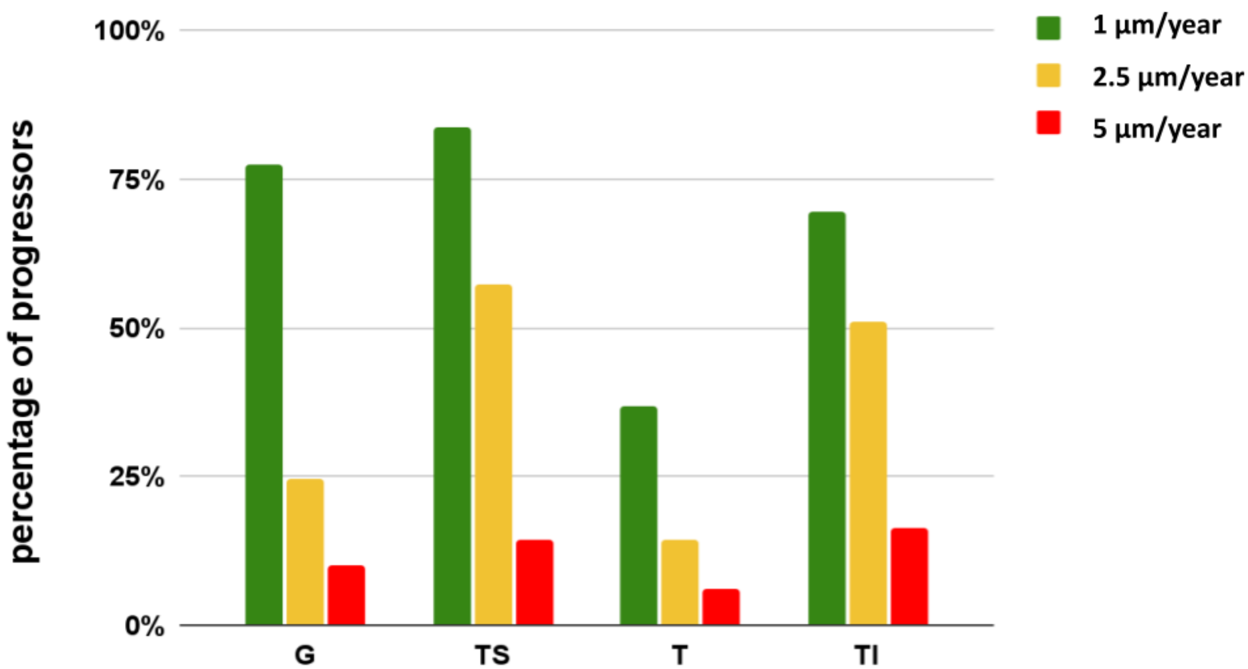

Figure 6: The percentage of progressors who had a retinal nerve fiber layer loss of at least 1 (green), 2.5 (yellow), and 5 (red) micrometers per year. G: global peripapillary region. TS: temporal-superior quadrant. T: temporal quadrant. TI: temporal-inferior quadrant.

Figure 7

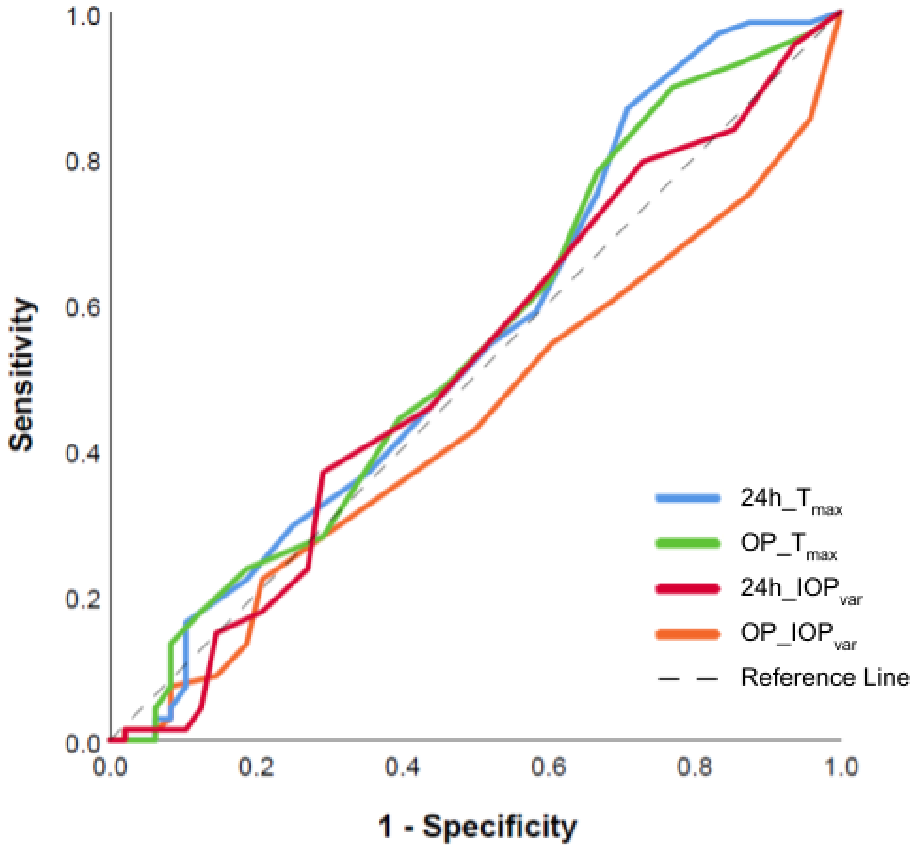

Figure 7. Receiver operating characteristic (ROC) curves comparing 24-hour and outpatient parameters of T_{max} and IOP_{var} for disease progression. IOP_{var} values of < 5 mmHg were excluded from the analysis. This figure shows a very low predictive power of disease progression for all parameters. Well-performing tests have a hyperbolic ROC curve with sensitivity and specificity close to 90%.

24h = nycthemeral measurements; OP = measurements during outpatient times.