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Prediction of glaucoma progression by 24-h contact lens sensor profile in patients with normal-tension glaucoma

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A single-center prospective cohort study was conducted to investigate whether intraocular pressure (IOP)-related 24-h contact lens sensor (CLS) profile parameters can help predict glaucoma progression in patients with normal-tension glaucoma (NTG). CLS measurements (Triggerfish; SENSIMED, Etagnières, Switzerland) at baseline without medication were performed for 24 h in one eye, following diurnal IOP measurements using Goldmann applanation tonometry at 3-h intervals. Glaucoma progression during the follow-up period of ≥ 2 years was determined based on the Guided Progression Analysis of Humphrey visual fields and/or structural progression using fundus photographs. Among 79 patients (mean values: follow-up periods, 48.1 months; age, 51.5 years; baseline IOP, 14.0 mmHg; mean deviation, – 6.04 dB), 23 showed glaucoma progression. A smaller standard deviation of nocturnal ocular pulse amplitude in the CLS profile, a larger range of diurnal IOP at baseline, and the presence of optic disc hemorrhage (DH) during the study period were significant risk factors for glaucoma progression in the multivariate Cox proportional hazards model (hazard ratio, 0.30/mVeq, 1.23/mmHg, and 4.37/presence of DH; P = 0.016, 0.017, and 0.001, respectively). CLS measurements may be useful for assessing the risk of future glaucoma progression in patients with NTG, providing supplementary information to routine IOP measurements.

Glaucoma is a leading cause of irreversible blindness globally[1]. The estimated global population affected by primary open-angle glaucoma in 2020 was around 70 million people aged over 40 years[2]. Although the pathogenesis of glaucomatous optic neuropathy (GON) is complex and multifactorial, the fluctuation and elevated levels of intraocular pressure (IOP) are representative triggers that cause mechanical damage to the retinal ganglion cells, resulting in glaucomatous visual field (VF) defects[3]. IOP-lowering treatment is the only proven way to slow down the progression of GON[4]. Therefore, a detailed IOP profile for each patient is crucial information for the diagnosis and treatment of glaucoma. Goldmann applanation tonometry (GAT), currently the gold standard method, is usually performed once during office hours to measure the IOP in patients with glaucoma. Given that approximately two-thirds of patients with glaucoma have peak IOP outside office hours[5], supplemental IOP measurements such as home tonometry are desirable for obtaining the diurnal profile of IOP levels and recording their fluctuation[6]. However, to date, there are no effective procedures for measuring ambulatory IOP throughout 24 h, except for devices that are implanted intraocularly[7].

Embedded strain gauges in the contact lens sensor (CLS) (Triggerfish; SENSIMED, Etagnières, Switzerland) capture changes in curvature at the corneal limbus[8]. The CLS values are not a direct indicator of the IOP levels but instead reflect changes in the volume of the eye caused by changes in IOP. The CLS 24-h profile comprises 288 median values obtained from measurements taken every 5 min over a 30-s period (known as "burst")[9]. High-frequency sampling at 10 Hz can capture transient IOP fluctuation caused by blinking, saccades, or ocular pulse amplitude (OPA, Fig. 1)[10]. IOP reduction through medical, laser, or surgical treatment was associated with changes in the CLS profile[11–14].

In glaucoma management, combining CLS information with a single tonometric reading, referred to as a "classifier," was found to be helpful in identifying patients with IOP levels exceeding the diagnostic threshold within 24 h[15]. In the study, the IOP of untreated patients with normal-tension glaucoma (NTG) was measured with tonometry every 3 h from 9:00 to 24:00, and a 24-h CLS measurement was performed on the following day.

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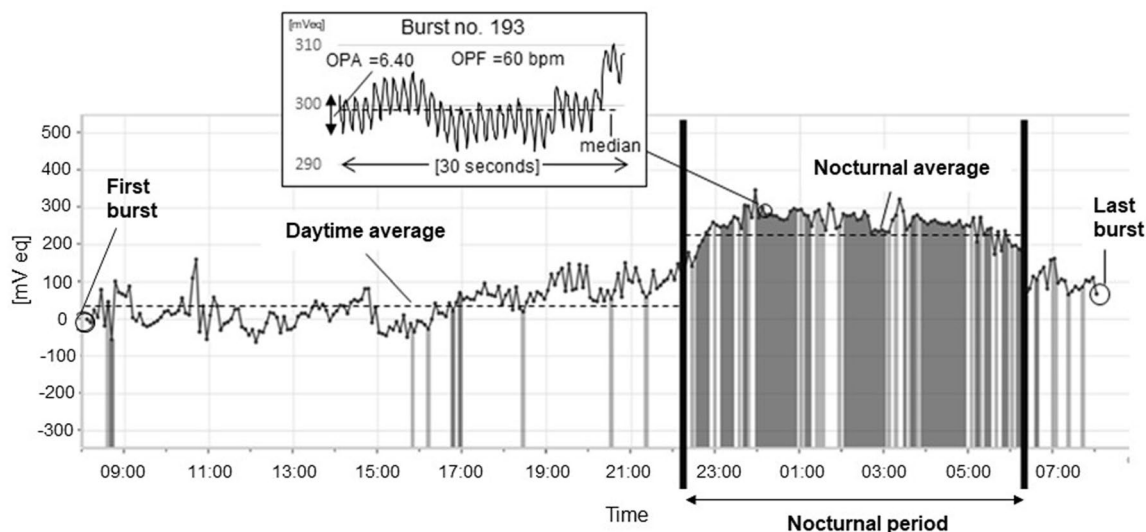
Fig. 1. An example of the 24-h contact lens sensor (CLS) profile. The y-axis represents the CLS output voltage (mVeq). The dark columns under the CLS plot indicate the sleeping periods judged by the CLS software based on the blinking frequency. Positions of the first and the last bursts are marked with open circles. Dashed lines indicate the daytime and nocturnal average CLS values. The inset displays the raw data for Burst number 193. Ocular pulse amplitude (OPA) is 6.40 mVeq and ocular pulse frequency (OPF) is 60 beats per minute. The median value is represented by the dashed line.

The "classifiers" at 15:00 and 18:00 demonstrated high sensitivity and negative predictive value (100%), correctly identifying all patients who had at least 1 IOP measurement of ≥ 20 mmHg. The CLS profile of untreated NTG patients differed from normal participants[16]. In the study, the standard deviation (SD) and the amplitude of the cosine-fit curve of the 24-h CLS measurements were significantly greater in NTG eyes than in healthy controls. The CLS profile fluctuation was smaller in eyes treated surgically for glaucoma than in medically treated eyes[17]. Moreover, various retrospective studies have demonstrated that CLS parameters are significantly linked with a more rapid deterioration in VFs in patients with medically treated glaucoma[18–21]. However, there have been no prospective studies on CLS parameters to identify predictors of glaucoma progression.

In view of the above, we investigated whether parameters of the IOP-related 24-h CLS profile would be relevant to subsequent glaucoma progression in patients with NTG in a prospective study.

Results

Demographics of study participants

A total of 100 patients with NTG were eligible and underwent CLS measurements. Of these, 10 patients were excluded from the analysis because of errors or problems during CLS data acquisition. Among the remaining 90 patients, 11 who were lost to follow-up within 2 years of baseline were excluded because of insufficient follow-up data. Eventually, 79 eyes from 79 patients were included in the study. The baseline and follow-up data are depicted in Table 1. The mean values of age, baseline IOP, and mean deviation of Humphrey Visual Field Analyzer (HFA) 24–2 VFs were 51.5 years, 14.0 mmHg, and -6.04 dB, respectively. A total of 38 (48.1%) eyes underwent a washout of glaucoma medication before CLS measurements. Of these, 8 (21.1%) and 15 (39.5%) patients experienced an increase and a decrease in the number of glaucoma medications compared to the pre-washout status, respectively. Only one patient (1.3%) among treatment-naïve patients remained off medication throughout the study period. A stacked column chart displaying the number of glaucoma medications during the study period is shown in Fig. S1. There were 31 (39%) eyes with the medication unchanged between pre-washout status and the follow-up period; 7 (23%) eyes showed glaucoma progression. In contrast, 48 (61%) eyes had an increase in medication during the follow-up periods compared to the pre-washout status. Among them, 16 (33%) eyes showed glaucoma progression. The proportion of eyes experiencing glaucoma progression did not differ significantly between eyes with and without changes in medication ($p = 0.44$).

Incidence of glaucoma progression

During mean follow-up periods of 48.1 months, 11 eyes showed VF progression judged with data of 10.0 ± 1.9 (6–14) VF sessions, while 15 were deemed to have structural progression based on fundus photography. Collectively, 23 (29.1%) of the 79 eyes of the 79 patients had glaucoma progression (VF and/or structural progression). None of the patients had any conditions that might influence the determination of glaucoma progression during the follow-up period, such as the development of clinically significant cataracts or intraocular surgeries. The Kaplan–Meier survival curve for the cumulative probability of glaucoma non-progression is shown in Fig. 2.

Baseline data	
Age, years	51.5 ± 12.2
Male/female	30/49
Right eye/left eye	42/37
Hypertension (yes/no)	16/63
Diabetes (yes/no)	3/76
Visual acuity (logMAR)	− 0.07 ± 0.04
VF MD (dB)	− 6.04 ± 3.58
VF PSD (dB)	7.48 ± 3.87
Spherical equivalent (diopter)	− 5.7 ± 3.2
Corneal curvature (mm)	7.8 ± 0.3
Axial length (mm)	26.0 ± 1.7
Corneal hysteresis (mmHg)	10.3 ± 1.2
Central corneal thickness (mm)	540.9 ± 25.9
Anterior chamber volume (mm^3)	172.9 ± 42.3
Circumpapillary retinal nerve fiber layer thickness (μm)	71.0 ± 12.9
Vertical cup-to-disc ratio measured by OCT	0.73 ± 0.10
Subfoveal choroidal thickness (μm)	200.4 ± 78.3
Diurnal mean IOP (mmHg)	14.1 ± 2.6
Range of diurnal IOP (mmHg)	3.9 ± 1.8
Follow-up data	
Follow-up periods (months)	48.1 ± 11.7
Number of VF sessions	10.0 ± 1.9
Disc hemorrhage during the study period (eyes)	17 (21.5%)
Mean IOP (mmHg) during the study period	13.8 ± 1.8
SD of IOP (mmHg) during the study period	1.6 ± 0.6
Mean number of glaucoma medications during the follow-up period	1.4 ± 0.7
Increase in the number of glaucoma medications during the follow-up period compared to the pre-washout status (yes/no)	48/31

Table 1. Baseline and follow-up data of study participants (n = 79). Mean ± SD is shown for numerical variables. logMAR: Logarithm of the minimal angle of resolution, VF: visual field, MD: Mean deviation, PSD: pattern standard deviation, OCT: optical coherence tomography, IOP: intraocular pressure, CLS: contact lens sensor, SD: standard deviation.
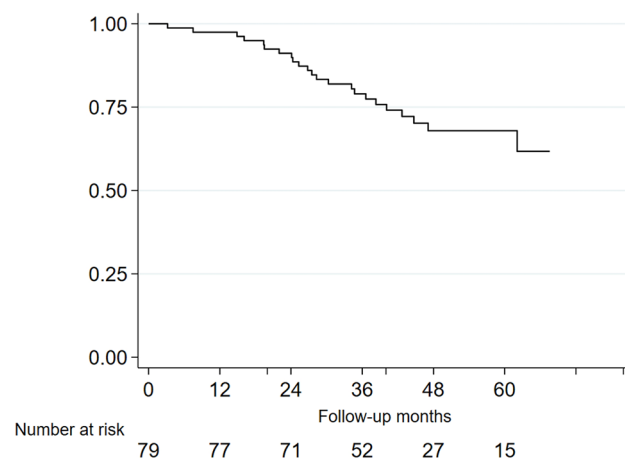

Fig. 2. Kaplan–Meier survival curve demonstrating the cumulative probability of glaucoma non-progression over time.

Factors associated with glaucoma progression

A comparison of various factors between eyes with and without glaucoma progression is shown in Supplementary Table S1. During the study period, optic disc hemorrhage (DH) occurred more frequently in eyes with glaucoma progression than in those without (P = 0.005). Table 2 shows univariate and multivariate Cox proportional-hazards models to identify factors associated with glaucoma progression. In the univariate analysis, DH found

Variables	Univariate Hazard ratio (SE), p-value	Multivariate Hazard ratio, (SE) p-value
Baseline variables		
Age (yrs)	0.98 (0.02), 0.21	
Sex (Ref. female)	1.49 (0.62), 0.34	
MD (dB)	0.99 (0.06), 0.85	
PSD (dB)	0.996 (0.05), 0.94	
Spherical equivalent (diopter)	0.94 (0.06), 0.36	
Corneal curvature (mm)	2.53 (1.92), 0.22	
Axial length (mm)	1.18 (0.15), 0.20	
Corneal hysteresis (mmHg)	0.82 (0.15), 0.28	
Central corneal thickness (mm)	0.995 (0.009), 0.53	
Anterior chamber volume (mm³)	1.004 (0.005), 0.38	
Circumpapillary retinal nerve fiber layer thickness (μm)	1.03 (0.02), 0.11	
Vertical cup-to-disc ratio measured by OCT	1.86 (3.80), 0.76	
Subfoveal choroidal thickness (μm)	0.998 (0.003), 0.41	
Diurnal mean IOP (mmHg)	1.08 (0.08), 0.34	
Range of diurnal IOP (mmHg)	1.20 (0.11), 0.057	1.23 (0.10), 0.016
20 CLS parameters		
Daytime average CLS (mVeq)	1.003 (0.003), 0.36	
SD of daytime CLS (mVeq)	1.006 (0.007), 0.41	
Nocturnal average CLS (mVeq)	1.001 (0.002), 0.59	
SD of nocturnal CLS (mVeq)	0.99 (0.02), 0.52	
24 h average CLS (mVeq)	1.003 (0.003), 0.29	
SD of 24 h CLS (mVeq)	1.0003 (0.006), 0.96	
Increase in nocturnal average CLS values relative to the daytime average (mVeq)	0.999 (0.003), 0.81	
Increase in CLS values in the last burst relative to the first burst (mVeq)	1.004 (0.002), 0.12	
Daytime average OPA (mVeq)	0.82 (0.09), 0.09	
SD of daytime OPA (mVeq)	0.62 (0.19), 0.13	
Nocturnal average OPA (mVeq)	0.92 (0.09), 0.40	
SD of nocturnal OPA (mVeq)	0.42 (0.21), 0.09	0.30, (0.15), 0.017
24 h average OPA (mVeq)	0.89 (0.10), 0.28	
SD of 24 h OPA (mVeq)	0.60 (0.22), 0.15	
Daytime average OPF (bpm)	0.98 (0.03), 0.51	
SD of daytime OPF (bpm)	0.98 (0.09), 0.82	
Nocturnal average OPF (bpm)	0.996 (0.03), 0.90	
SD of nocturnal OPF (bpm)	0.96 (0.18), 0.84	
24 h average OPF (bpm)	0.991 (0.03), 0.75	
SD of 24 h OPF (bpm)	0.99 (0.15), 0.93	
Variables at follow-up visits		
DH during the study period (Ref. no DH)	3.23 (1.36), 0.005	4.37 (1.92), 0.001
Mean IOP (mmHg) during the study period	0.89 (0.11), 0.36	
SD of IOP (mmHg) during the study period	1.41 (0.45), 0.29	
Mean number of glaucoma medications during the study period	0.97 (0.27), 0.91	
Increase in the number of glaucoma medications during the study period compared to the pre-washout status (Ref. no increase)	1.33 (0.61), 0.53	

Table 2. Factors associated with glaucoma progression (23/79 eyes progressed). Factors with $p < 0.2$ in the univariate analysis were entered in the multivariate analysis. The final multivariate model was obtained by backward selection until all p-values were < 0.05. Ref. indicates the reference group, and the reference interval is one unit (shown in parentheses). SE: standard error, MD: mean deviation, PSD: pattern standard deviation, OCT: optical coherence tomography, IOP: intraocular pressure, CLS: contact lens sensor, SD: standard deviation, OPA: ocular pulse amplitude, OPF: ocular pulse frequency, DH: disc hemorrhage.

during the study period was significantly associated with glaucoma progression (hazard ratio, 3.23, $P = 0.005$). The SD of nocturnal OPA in the CLS profile, range of diurnal IOP at baseline, and DH during the study period were significant risk factors for glaucoma progression in the multivariate Cox proportional hazards model (hazard ratio, 0.30/mVeq, 1.23/mmHg, 4.37/presence of DH; $P = 0.016, 0.017, 0.001$, respectively). Factors associated with either VF or structural progression only were also determined (Supplementary Tables S2 and S3). Multivariate analysis showed that longer axial length, increase in CLS values in the last burst relative to the first burst, and a

smaller SD of nocturnal OPA were significantly associated with progression by VF criteria only (hazard ratio, 1.87/mm, 1.009/mVeq, and 0.09/mVeq; $P = 0.004$, 0.017, and 0.022, respectively; Supplementary Table S2). In contrast, thicker circumpapillary retinal nerve fiber layer and DH occurrence during the study period were significant factors for structural progression only (hazard ratio, 1.05/μm, 3.88/presence of DH; $P = 0.027$, 0.010, respectively; Supplementary Table S3). All P values for explanatory variables in the multivariate models remained significant at a false discovery rate of 0.05.

Discussion

The present prospective study investigated whether parameters of the IOP-related 24-h CLS profile could help predict glaucoma progression in patients with untreated NTG. The major finding of this study was that the CLS parameter, the SD of nighttime OPA measured at baseline, was a significant predictor of subsequent glaucoma progression in patients with NTG when adjusted for DH occurrence during the study period and diurnal IOP fluctuation at baseline. Eyes with a smaller nighttime OPA SD were more likely to show glaucoma progression. Four retrospective studies have addressed the association between CLS parameters and glaucoma progression in patients with open-angle glaucoma[18–21]. All of them evaluated VF changes (i.e., MD slopes) as an outcome measure of glaucoma progression. Although the results of the four studies were variable, partly because of the differences in the CLS parameters examined, the study by De Moraes et al.[19], identified the CLS parameter, the SD of OPA at night, as one of the significant factors associated with faster glaucoma progression, which is consistent with our findings. In their study, the MD slope before CLS measurements was examined as an outcome measure of VF progression in 445 eyes of 445 patients with treated, manifested open-angle glaucoma at 50 study sites across 13 countries[19]. Of note, the SD of nighttime OPA was identified as a significant factor associated with the event-based VF progression in the supplemental multivariate analysis of our study (Table S1). Thus, two independent studies supported a smaller SD of nighttime OPA as a risk factor for VF progression, despite the different study designs (i.e., prospective vs. retrospective; event-based progression using Guided Progression Analysis vs. MD slope). Although OPA can be measured using tonometry such as the dynamic contour tonometer[22], continuous monitoring of OPA is currently only possible with CLS.

The reason why a smaller SD of nighttime OPA indicates subsequent glaucoma progression remains unknown. The OPA measured by tonometry reflects transient IOP changes due to fluctuations in ocular blood volume during the cardiac cycle. Zion et al. found that the pulsatility index of the choroid, as measured by color Doppler imaging, is strongly associated with OPA[23]. Given that the choroid receives strong autonomic innervation[24], choroidal blood flow may fluctuate in response to changes in autonomic tone according to the sleep stages composing a sleep cycle[25]. The smaller SD of nighttime OPA may indicate poor reactivity of choroidal vessels to autonomic tone during the sleep period due to impairments in the neural control of choroidal blood flow in eyes with glaucoma[24]. Another possibility is that the smaller SD of OPA may have resulted from a smaller amplitude of ocular volumetric changes in response to choroidal blood flow. In this regard, the SD of nighttime OPA had a significant positive correlation with the average OPA (Pearson correlation coefficient, $r = 0.69$, $P < 0.001$). However, the association between the SD of nighttime OPA and glaucoma progression was still significant after accounting for the average OPA (hazard ratio, 0.25/mVeq, $P = 0.044$). Furthermore, the average OPA itself was not significantly associated with glaucoma progression. Thus, the fluctuation in OPA during the sleep period was more significant for glaucoma progression than its average. A recent report from the United Kingdom Glaucoma Treatment Study investigated the association between OPA, measured multiple times using the dynamic contour tonometer during follow-up periods, and VF progression[26]. In the multivariate analysis, a larger OPA normalized for mean IOP was identified as a significant factor associated with faster pointwise rates of progression in the placebo arm. This suggests that OPA may be an independent factor for faster glaucoma progression.

This prospective study aimed to determine whether CLS parameters are helpful in predicting glaucoma progression. A previous study by Tojo et al. evaluated VF changes after CLS measurements as glaucoma progression[20]. The authors showed that several CLS parameters, such as the SD of CLS values, had a significant correlation with rapid VF progression. However, they did not examine the high-frequency CLS parameters, including OPA. They included patients with a history of intraocular surgeries, including non-filtering glaucoma surgery. Glaucoma medications may affect the 24-h profile of CLS values[11], which makes it difficult to determine whether the CLS changes are derived from intrinsic IOP-related changes or the effects of medication. However, no previous studies on glaucoma progression have measured CLS in patients under medication-free conditions. To minimize the effects of IOP-lowering drugs, we measured CLS values in the absence of glaucoma medication in this study.

In our study, DH was identified as a significant risk factor for both glaucoma progression and structural (i.e., fundus photography) progression, which is consistent with many previous studies[27]. Although the pathogenesis of DH has not been fully elucidated, it is reported to be closely associated with the site of active glaucoma progression in the optic disc[28,29]. The fluctuation of diurnal IOP was also significantly associated with glaucoma progression in this study. As regards the risk factor for glaucoma progression, there have been relatively few studies on short-term (i.e., diurnal) IOP fluctuations compared with long-term IOP fluctuation[30]. Although controversial[31], in a retrospective study of patients with NTG, Ishida et al. showed that IOP fluctuation at a 24-h phasing was one of the significant factors for VF deterioration[32]. Asrani et al. reported that larger fluctuations of diurnal IOP measured by home tonometry were a significant risk factor for subsequent VF progression in patients with glaucoma with baseline office IOP in the normal range[33]. Our results of a prospective cohort study with NTG patients thus become another piece of evidence that greater diurnal IOP fluctuations measured at baseline may be associated with a higher risk of glaucoma progression in the future.

Regarding the study limitations, given that this was a single-site study conducted in Japan, the participants were only Japanese. Hence, the study findings may not be applicable to other races or ethnicities. Because the study eyes mostly had NTG, the results may have been different in eyes with higher IOP. Further, the patients

were relatively young and myopic because the CLS recording was more acceptable for CL users and therefore may not represent older or emmetropic NTG patients. The background of the included patients is an inherent bias in the study design.

The study design was finalized in 2016, and structural progression was determined by subjective assessment using fundus photographs, given that photographic assessment has been the gold standard for determining the endpoint of glaucomatous structural progression in many clinical studies. In contrast, OCT provides a more quantitative and objective method than subjective assessment of optic disc photographs for measuring progression. Although OCT may produce inconsistent results for determining progression among different OCT devices and a definitive consensus on OCT progression criteria has yet to be established, studies using OCT to assess the progression of glaucoma have been increasing in recent years. Hence, future longitudinal studies using OCT to evaluate the relationship between CLS parameters and glaucoma progression are necessary.

In this study, we measured CLS profiles in the absence of glaucoma medication to minimize the effects of IOP-lowering drugs on the profiles. However, the differences in IOP levels at the time of CLS measurements and during the follow-up period may affect the relationship between the CLS profile and glaucoma progression. In this regard, the participants in this study were patients with NTG, and the diurnal mean IOP before CLS measurements was not significantly different from the mean IOP during the follow-up period ($p = 0.40$), even though 38 (48.1%) eyes underwent a washout of glaucoma medication before CLS measurements. For sensitivity analyses, if we excluded the 4 patients who had a diurnal mean IOP before CLS measurements more than 3 mmHg higher compared to the mean IOP during follow-up periods, the results of the multivariate Cox proportional hazards model remained almost unchanged (nocturnal SD of OPA, range of diurnal IOP at baseline, and presence of DH during the study period; hazard ratio, 0.30/mVeq, 1.40/mmHg, and 4.37/presence of DH; $P = 0.013$, 0.029, and 0.002, respectively). Furthermore, if we included the difference in IOP between the diurnal mean IOP before CLS measurements and the mean IOP during the follow-up periods as an explanatory variable in the multivariate Cox proportional hazards model involving all 79 patients, we found that nocturnal SD of OPA remained significant (hazard ratio, 0.31/mVeq; $P = 0.024$).

Glaucoma medication was initiated at the discretion of each physician during the follow-up period. Treatment might have affected the study outcome, although IOP and the number of glaucoma medications were not associated with glaucoma progression in our study cohort. Furthermore, when the variable, whether the number of glaucoma medications increased during the study period compared to the pre-washout status or not, was included as an explanatory variable along with nocturnal SD of OPA in the CLS profile, range of diurnal IOP at baseline, and the presence of DH during the study period, nocturnal SD of OPA remained significant (hazard ratio, 0.31/mVeq; $P = 0.025$). Given that the statistical analysis was performed by a study member who did not treat any participants, treating physicians had no information about the baseline testing of CLS, which should have no influence on their therapeutic decision.

Our study may lack sufficient power to detect other risk factors due to the small sample size. It cannot exclude the possibility that other unmeasured or residual confounding variables may explain our results. For example, a CLS parameter, mean peak ratio, was found to be a significant factor associated with MD changes in two previous studies[18,19]. Regarding the potential confounders, we conducted an additional analysis in which we included possible confounders of glaucoma progression such as age, baseline MD, central corneal thickness, mean IOP during the study period, and mean number of glaucoma medications during the study period as explanatory variables in the final multivariate Cox proportional hazard models for glaucoma progression. The results showed that all three variables remained significant: the SD of nocturnal OPA, range of diurnal IOP at baseline, and DH during the study period (hazard ratio, 0.34/mVeq, 1.21/mmHg, 4.70/presence of DH; $P = 0.038$, 0.043, and 0.002, respectively). This suggests that these potential confounders did not influence the findings. A multi-center prospective study with a larger sample size is necessary to confirm the findings of the present study.

In summary, we showed that the CLS parameter, SD, of nighttime OPA measured at baseline was a significant predictor of subsequent glaucoma progression in patients with NTG when adjusted for DH occurrence and baseline IOP fluctuation. This finding corroborates the results of a previous multicenter retrospective study[19]. CLS measurements may be useful for assessing the risk of future glaucoma progression in patients with NTG, providing supplementary information to routine IOP measurements.

Methods
Study participants
This was a single-center, prospective cohort study. From September 2016 to July 2020, participants were recruited from patients referred to the Department of Ophthalmology, Kanazawa University Hospital, for further examination or treatment of glaucoma. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Kanazawa University Hospital (2015-244). Written informed consent was obtained from all patients.

The inclusion criteria were as follows: age $\geq$ 20 years, NTG without glaucoma medication for at least 4 weeks. The glaucoma medication was washed out if needed. VF mean deviation $\geq$ − 15 dB by standard automated perimetry (HFA 24–2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Inc., Dublin, CA, USA), and best-corrected visual acuity of $\geq$ 0.8. Glaucomatous optic disc abnormalities corresponding to VF defects, normal open angle, and IOP $\leq$ 20 mmHg at outpatient visits were required to diagnose NTG. Glaucomatous VF defects were defined as follows: abnormal glaucoma hemifield tests, pattern standard deviation < 5%, and/or a cluster of three points with a probability < 5% on a pattern deviation map in at least one hemifield, including at least one point with a probability < 1%. Individuals with a history of eye surgery, ocular or systemic diseases (other than glaucoma) that may affect vision or sleep quality, ocular inflammation or trauma, mental illness, or shift work were excluded.

Study protocol

Patients meeting the eligibility criteria underwent ocular examinations that included measurements of their refractive power and corneal radius (ark-530a; Nidek, Inc., San Jose, CA, USA), axial length (OA-2000; TOMEY Corporation, Nagoya, Japan), corneal hysteresis (Ocular response analyzer; Reichert Ophthalmic Instruments, Depew, NY, USA), central corneal thickness and anterior chamber volume (Pentacam 70,700; Oculus GmbH, Wetzlar, Germany), HFA 24–2 VFs, and measurements of the thickness of the circumpapillary retinal nerve fiber layer and subfoveal choroid and of vertical cup-to-disc ratio using optical coherence tomography (RS-3000 Advance Retina Scan; Nidek Inc., Gamagori, Japan).

The CLS measurements at baseline were performed in eyes without medication during a 2-day hospitalization at Kanazawa University Hospital. The detailed study protocol was described in our previous study[15]. Briefly, IOP was measured using GAT in a sitting position at 3-h intervals from 09:00 to 24:00 on the first day. Next, CLS measurements were performed in the eligible eye on the second day at 08:30 a.m. for 24 h. If both eyes were eligible, CLS measurements were performed for the eyes with the worse VF.

The participants were followed up every 3 months for at least 2 years. Fundus photography and IOP measurements were performed every 3 months, and HFA 24–2 VFs were measured every 6 months. During the follow-up period, attending doctors initiated or resumed glaucoma treatment with IOP-lowering eye drops at their discretion based on the target IOPs.

Determination of glaucoma progression

The progression of glaucoma was determined based on VF and/or structural progression. The VF progression was based on the event-based analysis[30,34]. Only reliable VF data with fixation loss < 20%, false positive rate < 15%, and false negative rate < 20% were used. The "likely progression" by the Guided Progression Analysis (Carl Zeiss Meditec Inc., Dublin, CA), which is defined as a status with 3 or more VF locations that showed significant decreases in pattern deviation from the 2 baseline VF tests for ≥ 3 consecutive tests, was considered progression. The time when "likely progression" was flagged for the first time was defined as the time of progression.

For structural progression, fundus photographs from the baseline and the last visit were compared. Structural progression was defined as the widening or emergence of retinal nerve fiber layer defects, rim thinning, or enlarged cupping[28]. For eyes with progression, baseline photographs were later compared with those taken at other follow-up visits to determine when progression occurred. The time of progression was defined as the first visit, with progression occurring when the same change was observed on subsequent visits. The presence or absence of DH was recorded for each photograph, which was performed separately from the evaluation of structural progression[28]. Two glaucoma specialists (T. H. and S. O.) independently evaluated fundus photographs. If the two evaluators disagreed, another glaucoma specialist (K. S.) made the final judgment.

Statistical analysis

The primary objective of this study was to identify risk factors for the progression of glaucoma. Kaplan–Meier survival analysis was used to explore the time from baseline to glaucoma progression. The Cox proportional hazards model was employed to identify factors associated with glaucoma progression. The independent variables used for the univariate analysis were baseline factors (age, sex, VF indices, ocular parameters, and diurnal IOP data), 20 CLS parameters[9], and variables at follow-up visits (DH, IOP data, and the number of glaucoma medications). Variables with $p < 0.2$ in the univariate analysis were entered into the multivariate analysis. The final multivariate model was obtained by backward selection until all p-values were < 0.05. We checked for collinearity in the Cox proportional hazard models by looking at the correlation matrix of coefficients. When a coefficient exceeded the level of 0.70, we removed one of the highly collinear variables from the model and performed backward selection separately. We confirmed that the final models did not have any coefficients indicating high collinearity.

Cox proportional hazard models with event definitions of either VF or structural progression were also used. Comparisons between eyes with and without glaucoma progression were performed using linear regression for numerical variables, and the Fisher's exact test was employed for categorical variables.

Based on previous studies, the sample size was determined as follows: In a prospective cohort study of 195 eyes from 115 Japanese patients with primary open-angle glaucoma and a baseline IOP of 18 mmHg or less on monotherapy with prostaglandin analogs, 33% of eyes showed progression either by fundus photography or VFs using the Guided Progression Analysis during a 3-year follow-up period[28]. Based on a one-sided alpha error level of 0.05, a SD of 0.50, a power of 0.80, an event probability of 0.33, and a coefficient (log hazard ratio) of 1 (which is equivalent to a hazard ratio of 2.7182), the estimated sample size for the Cox proportional hazards model with a nonbinary covariate was 75 with an estimated number of events of 25[35]. Accordingly, we planned to conduct CLS measurements for 100 participants and to follow up for a mean period of ≥ 3 years. All statistical analyses were performed using STATA software (version 17.0, StataCorp, College City, TX, USA), and the statistical significance level was set at $P < 0.05$. In the multivariate models, the significance of P-values was determined using the Benjamini–Hochberg method to control the false discovery rate at 0.05.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare no competing interests.

Additional information

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