# Biomechanical Glaucoma Factor and Corneal Hysteresis in Treated Primary Open-Angle Glaucoma and Their Associations With Visual Field Progression

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**Purpose.** To investigate the relationship between biomechanical glaucoma factor (BGF) measured with Corvis ST and glaucomatous visual field (VF) progression, compared to corneal hysteresis (CH) measured with ocular response analyzer using a longitudinal dataset of primary open-angle glaucoma (POAG). The discriminative powers of BGF and CH were also compared using a cross-sectional dataset.

**Methods.** The longitudinal dataset included 166 POAG eyes. The rate of VF change during the follow-up period was evaluated using the mean of 52 pointwise total deviations in the Humphrey 24-2 field test. Variables associated with the VF progression rate were identified from BGF, CH, age, baseline VF severity, and intraocular pressure during the VF follow-up period by identifying the optimal model. The cross-sectional dataset included 68 POAG eyes and 68 healthy eyes. Using this dataset, the area under the curve (AUC) values of the receiver-operating curve were compared between CH and BGF.

**Results.** The optimal multivariate linear mixed model to describe the VF rate included age and CH, but not BGF. Between POAG and healthy eyes, CH was statistically different ($P < 0.001$), although this was not the case with BGF. The AUC values were 0.61 and 0.71 for BGF and CH, respectively ($P = 0.027$).

**Conclusions.** CH, but not BGF, was associated with VF progression in POAG patients under treatment. BGF was not useful to discriminate POAG between treated and normal eyes.

Keywords: glaucoma diagnosis, corneal biomechanics, biomechanical glaucoma factor, corneal hysteresis, glaucoma progression

Intraocular pressure (IOP) is a major contributor of glaucoma development and progression.[1,2] However, visual field (VF) progression can be observed in 20% of patients with primary open-angle glaucoma (POAG), even after a 30% reduction in IOP.[3] A wide range of VF progression rates in POAG eyes in the real-world setting cannot be fully explained based only on the IOP.[4] Therefore, the variables related to VF progression in patients with glaucoma, other than IOP, must be examined.

Corneal biomechanical properties are good examples of such variables and can be measured with two clinical devices currently. Corneal hysteresis (CH), measured using the ocular response analyzer (ORA; Reichert Inc., Depew, NY), reflects damping capacity of the cornea.[5] Low CH is associated with the diagnosis,[6] development,[7] severity,[8] and progression of glaucoma.[9,10] Furthermore, a prospective study indicated the effect of IOP on rates of VF progression depended on CH.[9] By contrast, the clinical application of an ultra-high-speed Scheimpflug camera provides detailed images of the corneal deformation induced by the application of an air jet in the corneal visualization Scheimpflug technology (Corvis ST, Oculus GmbH, Wetzlar, Germany). This yields a number of corneal dynamic response parameters; our previous studies suggested the usefulness of such parameters when analyzing the severity[8] and VF progression[11] of POAG.

Very recently, a novel Corvis ST-related parameter (biomechanical glaucoma factor [BGF]) was developed to

distinguish the eyes with normal tension glaucoma (NTG) from healthy eyes by calculating the optimal combination of Corvis ST parameters.[12] However, the usefulness of BGF was merely validated through an internal cross-validation (three folds) in a single dataset (70 healthy individuals and 70 NTG patients). Moreover, the association of BGF with VF progression has not been investigated. In particular, the usefulness of BGF in a broader glaucoma subtype, such as POAG, has not yet been examined, and thus requires assistance in interpreting BGF in terms of biomechanical properties that are involved in disease pathogenesis.

The present study aimed to evaluate relationships between rates of VF change and values of BGF and CH in POAG under treatment, using a longitudinal dataset. The discrimination abilities of BGF and CH between POAG and normal control eyes were also compared, using a cross-sectional dataset.

## Method

A total of 192 eyes of 134 POAG patients and 68 normal eyes of 68 people, obtained at the University of Tokyo Hospital, Osaka University, and Seirei Hamamatsu General Hospital, were included in this retrospective study. The Research Ethics Committees of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo, Osaka University, and Seirei Hamamatsu General Hospital approved this study. All participants signed a written informed consent for their clinical information to be stored in the hospital database and used for research. The present study was conducted according to the tenets of the Declaration of Helsinki.

POAG was diagnosed using the following criteria: (1) typical glaucomatous changes in the optic nerve head (ONH), such as a rim notch with a rim width of $\leqq$0.1 disc diameters or a vertical cup-to-disc ratio of >0.7, and/or a retinal nerve fiber layer defect with its edge at the ONH margin greater than a major retinal vessel; (2) glaucomatous VF defects compatible with the ONH changes that fulfill the Anderson-Patella criteria[13] on two consecutive occasions; (3) the absence of systemic or ocular history or existing factors that could explain glaucomatous change or raised IOP.

The healthy control group included participants with no abnormal eye-related findings except for clinically insignificant senile cataract and no history of ocular diseases. This healthy control group served as the normal control in the cross-sectional analysis, which is described later.

Subjects were excluded if they presented systemic or ocular conditions that affect intraocular pressure or visual field. These include a history of systemic corticosteroid, narrow angle, clinically significant cataract, and ocular surgeries (except for uneventful intraocular lens implantation). Patients younger than 20 years old were also excluded. POAG eyes under topical medication were not excluded.

Corvis ST and ORA measurements were conducted on the same day with a 15 minute interval between the two measurements. The order of the measurements was randomly determined. The axial length was measured using the IOLMaster, ver. 5.02 (Carl Zeiss Meditec, CA). IOP was measured with a Goldmann applanation tonometer throughout the observation period. VF was measured using the Humphrey Field Analyzer II (Carl Zeiss Meditec Inc., Dublin, CA) either with a 24-2 or 30-2 SITA-standard program. Reliable VF was defined as the fixation loss, false-positive results, and false-negative results less than 33%.

### Corvis ST Measurement

The principles of Corvis ST measurements were described thoroughly elsewhere.[14] The high-speed Scheimpflug camera records 140 images of the cornea with a transient indentation in 30 ms after the application of an air impulse. The corneal response is characterized by two applanations during the inward and outward corneal movements, respectively; the highest concavity (HC) is defined as the maximal displacement of the corneal apex. Parameters provided by the current version of the Corvis ST software (software version 1.6r2036) include applanation length, velocity, and time of the two applanations; corneal deflection amplitude, radius, and time at HC; and several biomechanical indices calculated using the software. Some of the parameters relevant to BGF derivation are described below. Corvis ST measurements were conducted thrice, and the results were averaged. Only reliable Corvis ST measurements were used, based on the "OK" quality index displayed on the device monitor.

BGF was calculated using the formula below:[12]

$$Beta = 34.128 + 2.64 \times DARatioProg - 0.641 \times HCTime - 0.049 \times PachySlope - 0.202 \times bIOP - 0.036 \times CCT$$

$$BGF = \frac{EXP(Beta)}{EXP(Beta) + 1}$$

- DARatioProg: "Deformation amplitude ratio progression" represents the increase ratio of the deformation amplitude from the corneal apex toward the periphery. Higher DARatioProg values indicate a stiffer cornea.[12]
- HC time: "Highest concavity time" refers to the timing of the highest concavity.
- PachySlope: "Pachymetry slope" represents the difference in corneal thickness from the corneal apex toward the periphery. A smaller PachySlope indicates a relatively thin cornea in the periphery compared with that in the central region.
- CCT stands for "Central corneal thickness."
- bIOP: "Biomechanical IOP" is described as the corrected estimate of IOP obtained using the Corvis ST following the finite element method, adjusted for CCT and age variations.[15]

BGF ranges from 0 to 1; a higher value indicates a higher possibility of glaucoma.[12]

### ORA Measurement

Details of the ORA measurement are summarized elsewhere.[16] The ORA records two applanation pressures, namely, prior to and following an indentation of the cornea after the application of a rapid air jet. Because of its viscoelastic property, the cornea dissipates a part of the energy given off the air jet, resulting in a delay in the outward corneal movement and thus causing the difference in the pressures at the inward and outward applanation. This difference is called CH.[17] The ORA measurement was conducted thrice. Only the measurements with a quality index of >7.0 were used, and the average value was used in the analysis.

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## Statistical Analysis

**Longitudinal Analysis (VF Progression Analysis).** A longitudinal dataset comprising 166 eyes of 108 POAG patients was used to examine the association of BGF/CH with VF progression. POAG eyes were included in this dataset if they had at least eight reliable VFs, excluding the initial VF, for a minimum period of four years. Topical prostaglandin analogue use throughout the VF follow-up was also required to adjust for the potential influence of the therapeutics on corneal biomechanical measures, as was reported.[18–20]

We used the mean total deviation (mTD) of the 52 test points overlapping with the 24-2 HFA test to estimate the progression. The mTD progression rate was evaluated by linearly regressing mTD values against time using the latest eight VFs. Linear mixed models were used to investigate the relationship between the mTD progression rate and the BGF, CH, CCT, axial length, baseline age, baseline mTD at first VF, and mean IOP throughout the period where eight VFs were examined. As both eyes of patients were included in the longitudinal dataset and measurements would be highly correlated, each patient was regarded as having a random effect. This condition was modeled by fitting a linear model using the maximum likelihood method with a varying-intercept group effect. Then, model selection was used to identify the optimal linear mixed model for the mTD progression rate according to the second-order of the bias-corrected Akaike information criterion index (AICc), from all two[7] patterns using the seven tested variables. The AIC is a well-known statistical measurement used in model selection. The AICc is a corrected version of the AIC, which provides an accurate estimation even when the sample size is small.[21] The detail of AICc is described later in this section.

**Cross-Sectional Analysis (Comparison of CH and BGF Between Normal and Glaucoma Eyes).** For this purpose, a cross-sectional dataset was used, which comprised 68 eyes of 68 POAG patients (POAG group) and 68 eyes of 68 healthy people (normal group) who underwent Corvis ST and ORA measurements. One eye was randomly selected for the analysis if both eyes satisfied the inclusion criteria. The two groups were matched for number of eyes and age. The values of CH, BGF, and five Corvis ST parameters comprising BGF were compared between normal and POAG eyes. The discrimination ability of BGF was investigated through the area under the receiver operating characteristics curve (AUC) using a method by Delong et al.[22] for a comparison with CH. To better understand the mechanism of BGF on the diagnosis of glaucoma, variables that were useful for discriminating POAG eyes from normal eyes were identified by selecting the optimal multivariate logistic regression model with AICc, among five parameters comprised BGF (DARatioProg, HC time, PachySlope, CCT and bIOP), where the logistic model was assumed to have a linear relationship between the predictor variables and log-odds of POAG involvement.

In a multivariate regression model, the degrees of freedom decreases as the number of variables increases; hence, model selection methods should be used for better model fitting by removing redundant variables.[23,24] A decrease in the AICc values suggests an improvement of the model; the relative likelihood that a model ($model_x$ with $AICc_x$) minimizes information loss compared with a model with the smallest AICc ($model_{min}$ with $AICc_{min}$) was calculated as exp $((AICc_{min} - AICc_x)/2)$.[25]

**Table 1.** Baseline Demographics of the Longitudinal Dataset

| Variable | Longitudinal Group |
|---|---|
| Age (years old) | 59.1 ± 10.9 (32 to 82) |
| CCT (μm) | 524 ± 36 (455 to 623) |
| BGF | 0.53 ± 0.25 (0.093 to 1.00) |
| CH (mmHg) | 9.0 ± 1.2 (6.4 to 12.6) |
| Initial mTD (dB) | −7.25 ± 6.36 (−25.56 to 1.73) |
| Follow-up period (year) | 6.25 ± 2.00 (4.05 to 16.17) |
| mTD progression rate (dB/year) | −0.26 ± 0.43 (−2.67 to 0.59) |
| Mean IOP with GAT (mmHg) | 13.1 ± 2.1 (7.6 to 19.0) |
| Axial length (mm) | 25.68 ± 1.56 (22.30 to 29.20) |

Values are presented as median ± standard deviation (range).

BGF: biomechanical glaucoma factor; CCT, central corneal thickness; CH: corneal hysteresis; GAT: Goldmann applanation tonometry; mTD: mean total deviation.

**Table 2.** Univariate Relationship Between mTD Progression Rate and Various Parameters of the Longitudinal Dataset

| Variable | Coefficient | SE | *P* Value | AICc |
|---|---|---|---|---|
| Age (years old) | −0.0076 | 0.0033 | 0.026* | 173.16 |
| CCT (μm) | 0.00058 | 0.0011 | 0.59 | 178.04 |
| BGF | −0.24 | 0.15 | 0.11 | 175.70 |
| CH (mmHg) | 0.072 | 0.031 | 0.023* | 172.88 |
| Initial mTD (dB) | −0.00025 | 0.0052 | 0.96 | 178.34 |
| Mean IOP with GAT (mmHg) | −0.0048 | 0.018 | 0.79 | 178.27 |
| Axial length (mm) | 0.014 | 0.024 | 0.57 | 178.01 |

*: $P < 0.05$.

BGF: biomechanical glaucoma factor; CCT, central corneal thickness; CH: corneal hysteresis; GAT: Goldmann applanation tonometry; mTD: mean total deviation.

Holm's method was used to adjust the *P*values for the problem of multiple testings.[26] The statistical programming language "R" (R version 3.3.1; the foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses.

# Results

## VF Progression Analysis (Longitudinal Analysis)

The longitudinal dataset included 166 eyes of 108 patients. The demographics for this dataset are shown in Table 1. The univariate relationship between the mTD progression rate and various parameters are shown in Table 2. Age and CH were significantly related to the mTD progression rate ($P = 0.025$ and 0.027, respectively; linear mixed model), but BGF was not ($P = 0.61$). The optimal model for the mTD progression rate was as follows: mTD progression rate = $-0.53 - 0.0065 \times$ age $+ 0.062 \times$ CH (AICc = 172.27). The relative likelihood that a null hypothesis (a model without covariates; AICc = 176.24) minimizes information loss compared with the optimal model was 0.083.

## Comparison of CH and BGF Between Normal and Glaucoma Eyes

The cross-sectional dataset included 68 eyes of 68 POAG patients and 68 eyes of 68 healthy subjects. Forty-two eyes of 42 patients with POAG were derived from the longitudinal dataset. The baseline demographics of this dataset are shown in Table 3. The two groups were matched for age ($P = 1$). BGF was not significantly different between the

**Table 3.** Baseline Demographics of the Cross-Sectional Dataset

| | All | POAG | Normal | *t*-Test |
|---|---|---|---|---|
| Age (years old) | 69.2 ± 13.6 (27 to 97) | 69.1 ± 13.4 (27 to 92) | 69.4 ± 13.9 (27 to 97) | n.s. |
| BGF | 0.56 ± 0.27 (0.02 to 1) | 0.61 ± 0.26 (0.02 to 1) | 0.51 ± 0.27 (0.03 to 1) | 0.27 |
| CH (mmHg) | 9.4 ± 1.4 (6.3 to 12.4) | 8.9 ± 1.2 (6.3 to 11.6) | 9.9 ± 1.3 (6.6 to 12.4) | 0.00018* |
| bIOP (mmHg) | 13.1 ± 2.9 (7.9 to 27.8) | 12.9 ± 3.2 (7.9 to 27.8) | 13.3 ± 2.5 (8.8 to 21.4) | n.s. |
| DARatioProg | 0.72 ± 2.8 (−0.31 to 30.17) | 0.51 ± 1.21 (−0.31 to 8.82) | 0.93 ± 3.77 (−0.18 to 30.17) | n.s. |
| HC time (ms) | 17.15 ± 0.46 (15.83 to 18.23) | 17.13 ± 0.52 (15.83 to 18.23) | 17.17 ± 0.39 (16.28 to 17.92) | n.s. |
| CCT (μm) | 529 ± 37 (436 to 622) | 527 ± 38 (436 to 621) | 532 ± 36 (454 to 622) | n.s. |
| PachySlope | 39.3 ± 12.0 (7.8 to 81.6) | 35.5 ± 10.8 (7.8 to 58.5) | 43.1 ± 12.0 (14.6 to 81.6) | 0.0014* |
| Axial length (mm) | 24.44 ± 1.73 (21.17 to 29.53) | 25.04 ± 1.7 (21.63 to 28.76) | 24.01 ± 1.63 (21.17 to 29.53) | 0.020* |

Values are presented as median ± standard deviation [range]. n.s.: not significant.
*: $p < 0.05$ BGF: biomechanical glaucoma factor; CCT, central corneal thickness; CH: corneal hysteresis; GAT: Goldmann applanation tonometry; mTD: mean total deviation.
Axial length was not available for 12 eyes and 26 eyes in healthy control and POAG, respectively.

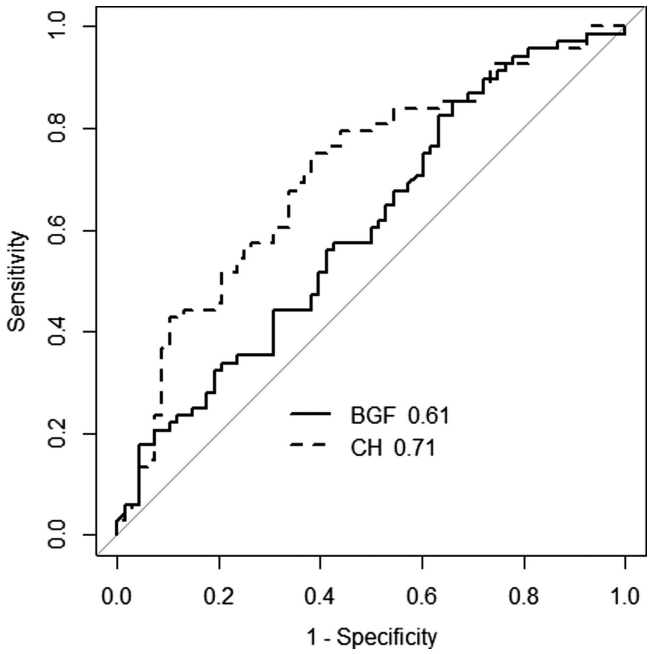


**Figure.** Receiver operating characteristic curves of BGF and CH for discriminating POAG eyes from normal eyes.

two groups ($P = 0.27$). PachySlope and CH were significantly lower ($P = 0.0014$, 0.00018, respectively) in POAG eyes than in healthy eyes. Of the 68 POAG eyes, 64 were under some topical anti-IOP medication. In particular, 56, 40, and 32 POAG eyes were treated with topical prostaglandin analogue, beta blocker, and carbonic anhydrase inhibitor, respectively.

The receiver operating characteristic curves of BGF and CH for discriminating POAG eyes from normal eyes are shown in Figure. The AUC value was 0.61 (95% confidence interval [CI]: 0.51–0.70) and 0.71 (95% CI: 0.62–0.80) for BGF and CH, respectively. The two AUC values were significantly different ($P = 0.027$ with Delong's method).

An optimal multivariate logistic regression model to discriminate POAG eyes from healthy eyes, identified using AICc, where predictor variables were selected from five parameters comprising BGF, was: $\log(P/(1-P)) = 2.39 - 0.061 \times \text{PachySlope}$, where $P$ stands for the probability that an eye has POAG. This gives an explicit formula for $P$: $P = 1/(1 + \exp(2.39 - 0.061 \times \text{PachySlope}))$ (AICc = 177.85). The odds ratio of PachySlope was 0.94 (95% CI: [0.91, 0.97]).

## Discussion

In the present study, the relationship between BGF, in comparison to CH, and VF progression rate in POAG was examined using eight VFs from 166 eyes of 108 participants. Age and CH were included in the optimal model to determine the mTD progression rate. In addition, the differences in BGF and CH between POAG and normal eyes were investigated using a cross-sectional dataset. CH had a higher AUC value than that of BGF.

BGF is a novel Corvis ST index that was constructed to distinguish eyes with OAG (NTG) from normal eyes.[12] The reported AUC to distinguish glaucoma eyes from normal eyes was 0.81. The present study reported a relatively lower AUC value (0.61). CH is an established risk factor for glaucoma development and progression.[5–10] In the present study, the AUC of CH was 0.71 and was significantly higher than that of BGF. Our results suggested that BGF is not useful in diagnosing POAG in the current population, which may be due to the broader background of glaucoma patients (POAG, not only NTG) in contrast to the original study in which BGF were developed,[12] as discussed later.

A multivariate analysis of the longitudinal dataset suggested that BGF was not significantly associated with glaucoma progression. This could be because BGF was derived from cross-sectional data.[12] Age and CH were significantly associated with VF progression, which is consistent with the findings of several studies demonstrating the association of CH[9,10] with glaucoma progression. Previous studies suggest that CH reflects the damping capacity of the cornea[5,17,27]; the eyes with higher CH may have an ONH structure that protects the optic nerve axons from external stress such as IOP, thus preventing glaucoma progression.[28–32] Furthermore, the correlation between CH and VF progression may be accounted for by the correlation between CH and (measured) IOP; that is, CH is correlated with a real IOP and also affects IOP measurement.[33] The absence of IOP in the optimal linear mixed model does not indicate IOP is not associated with the progression of VF, because the effect of IOP may be masked by the inclusion of CH in the optimal model. In addition, the currently analyzed patients were under IOP-reduction treatment. Indeed, both progression rate and mean IOP in the longitudinal dataset were

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rather low: –0.26 ± 0.43 dB/year and 13.13 ± 2.07 mmHg, respectively. These values were even lower than those reported in several recent studies, which indicated the VF progression rate based on the data obtained in real-world settings. Heijl et al. reported a VF progression rate of −0.80 dB/year (mean IOP: 18.1–20.2 mmHg), obtained from 583 OAG patients.[34] De Moraes et al. reported a −0.45 dB/year VF progression rate (mean IOP: 15.2 mmHg), obtained from 587 glaucoma patients.[35] Low IOP and resulting slow VF progression could make less detectable the association of the investigated parameters.

BGF was empirically derived from five Corvis ST measurements in NTG patients and normal controls; thus, it is not easy to interpret the medical mechanism. In particular, the relationship between the five Corvis ST variables and glaucoma remains inexplicable compared with that between CH and glaucoma. Analysis of the cross-sectional dataset revealed that lower PachySlope value was significantly correlated with the diagnosis of POAG. A lower PachySlope indicates more homogeneity in the thickness of the cornea, which is more common in eyes with NTG than in those with ocular hypertension.[36] However, other variables, including CCT, DARatioProg, and HCtime, were not significantly different between the POAG and healthy control eyes. This is in disagreement with the study by Karin et al; the NTG population had lower CCT than that of the normal controls.[12] It has been suggested that a thinner CCT increases the likelihood of conversion from ocular hypertension to glaucoma.[1,2] CCT has a significant effect on the Goldmann applanation tonometry measurement, which leads to an underestimation of the IOP. Furthermore, a thin CCT has been reported as an independent risk factor for glaucoma development (even when correcting for an underestimation of IOP).[37] The current population has a CCT that is similar to that of the healthy controls, probably due to the broader glaucoma subtype with different baseline IOP before treatment was administered. This may have weakened the relationship between BGF and POAG. DARatioProg and HCtime should be influenced not only by corneal biomechanical properties like stiffness itself[12] but true IOP, as was suggested from the reported influence of IOP on Corvis ST dynamic corneal response parameters.[38,39] Thus, Karin et al. claimed that BGF should include bIOP for adjustment.[12] In the current dataset, POAG eyes indeed had a similar bIOP value of 13.06 mmHg compared with that in their report (13.5 mmHg for NTG eyes); however, it should be noted the current POAG population was already under IOP-reduction treatments, and the unavailable baseline IOP would have been higher. The lowered IOP, together with changes in other biomechanical measures such as DARatioProg and HCtime, may have weakened the potential relationship between BGF and POAG. To summarize, a broader range of the glaucoma population was being treated to induce lower IOP, which could have masked the possible BGF difference between POAG eyes and normal eyes. Our findings should be corroborated in a future study that compares untreated POAG and NTG cases to shed light on a potential different pathogeneses that occur between NTG and broader POAG.

The present study has some limitations. Our population probably included both POAG and NTG patients. We could not distinguish them because the baseline IOP value was not available; many of the patients who referred to our hospitals from other clinics had already undergone IOP-reduction therapy. However, most of the cases analyzed were NTG cases due to the mean IOP level (13.13 mmHg) in the longitudinal dataset being considerably low. This is a glaucoma subtype common in Japanese individuals. A representative survey of the prevalence of glaucoma in Japan reported that 92% of POAG cases was NTG.[40] Another limitation of the present study is the effect of anti-glaucoma eye drops on the corneal biomechanical properties. Of the POAG population that were included in the cross-sectional study, 82.4% (56 out of 68 eyes) used a prostaglandin analogue, which was similar to a previous report (82%).[12] Anti-IOP agents can alter the cornea's biomechanical properties[41–43]; in particular, clinical studies have demonstrated that chronic use of a topical prostaglandin analogue significantly affects CH.[18–20] This implies that there are similar effects on Corvis ST-related parameters, such as BGF, because it also uses air jet applications. We conducted this study to compare BGF with CH using POAG patients under treatment, following a method used in a previous study[12]; however, a future study should investigate the usefulness of BGF in diagnosing glaucoma using untreated patients. Moreover, due to the high prevalence of myopia in Japan,[44] the current population included a relatively large proportion of myopic eyes (Table 1 and 3). Myopic eyes reportedly exhibited a different response to ORA and the Corvis ST measurement[45–47]; thus, the effect of the refraction status should be investigated in a future study.

In conclusion, CH was significantly associated with VF progression in POAG eyes undergoing treatment, but BGF was not. CH had a higher AUC value than BGF. The discriminative power of BGF should be validated further with treatment-naïve cases.

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