Clinical characteristics of glaucoma patients with various risk factors

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Abstract

Background: Glaucoma is multifactorial, but the interrelationship between risk factors and structural changes remains unclear. Here, we adjusted for confounding factors in glaucoma patients with differing risk factors, and compared differences in structure and susceptible areas in the optic disc and macula.

Methods: In 458 eyes with glaucoma, we determined confounding factors for intraocular pressure (IOP), central corneal thickness (CCT), axial length (AL), LSFG-measured ocular blood flow (OBF), which was assessed with laser speckle flowgraphy-measured mean blur rate in the tissue area (MT) of the optic nerve head, biological antioxidant potential (BAP), and systemic abnormalities in diastolic blood pressure (dBP). To compensate for measurement bias, we also analyzed corrected IOP (cIOP; corrected for CCT) and corrected MT (cMT; corrected for age, weighted retinal ganglion cell count, and AL). Then, we determined the distribution of these parameters in low-, middle-, and high-value subgroups and compared them with the Kruskal–Wallis test. Pairwise comparisons used the Steel–Dwass test.

Results: The high-cIOP subgroup had significantly worse mean deviation (MD), temporal, superior, and inferior loss of circumpapillary retinal nerve fiber layer thickness (cpRNFLT), and large cupping. The low-CCT subgroup had temporal cpRNFLT loss; the high-CCT subgroup had low cup volume. The high-AL subgroup had macular ganglion cell complex thickness (GCCT) loss; the low-AL subgroup had temporal cpRNFLT loss. The high-systemic-dBP subgroup had worse MD, total, superior, and inferior cpRNFLT loss and macular GCCT loss. The low-BAP subgroup had more male patients, higher dBP, and cpRNFLT loss in the 10 o’clock area. The high-OBF subgroup had higher total, superior and temporal cpRNFLT and macular GCCT.

Conclusions: Structural changes and local susceptibility to glaucomatous damage show unique variations in patients with different risk factors, which might suggest that specific risk factors induce specific types of pathogenesis and corresponding glaucoma phenotypes. Our study may open new avenues for the development of precision medicine for glaucoma.

Keyword: Risk factors, Optical coherence tomography, Individual treatment for glaucoma, Blood pressure, Glaucoma

Background

Glucoma is a multifactorial disease [1] with various reported risk factors, including high intraocular pressure (IOP), aging, myopia, [2] family history, [3] thin corneal central thickness (CCT) and corneal hysteresis, low ocular blood flow (OBF), abnormality of the lamina cribrosa, oxidative stress, neuroinflammation, and lifestyle factors, such as diabetes, sleep apnea, diet, and smoking [1, 4–9]. Lowering IOP is the only evidence-based treatment for...
preventing glaucoma progression, [10] but other risk factors are likely also involved in retinal ganglion cell (RGC) loss in glaucoma, acting via various pathways. IOP-lowering treatments are highly developed, including innovative eye drops with novel IOP-lowering mechanisms, minimally invasive surgical devices, and laser treatment. Nevertheless, the increasing number of patients with glaucoma-induced blindness is a serious problem in aging societies [11]. Therefore, there is a need for new treatments based on the pathophysiology of glaucoma. Specifically, there is an unmet medical need to prevent blindness in patients with glaucoma caused by non-IOP factors.

Previous epidemiological studies have shown that systemic OBF is deeply involved in the prevalence, development, and progression of glaucoma [1, 5, 12, 13]. Laser speckle flowgraphy (LSFG) clearly shows that optic nerve head (ONH) tissue-area mean blur rate (MT) significantly decreases in preperimetric glaucoma (PPG), [14] and that the peak of the LSFG waveform is delayed in early glaucoma [15]. We have also found, in an observational study of PPG, that low OBF is an important risk factor for glaucoma progression [16]. The loss of retinal nerve fibers reduces capillary density in the retinal nerve fiber layer (RNFL), a phenomenon that has led to much discussion as to whether decreased OBF is the primary or secondary event in glaucoma, i.e., whether it occurs before or after the onset of visual field defects. Recently, we made two very interesting findings. First, in glaucoma patients that we identified as having primary decreased OBF by adjusting for confounding factors, low OBF was associated with a larger optic disc cupping and a greater incidence of damage in the macula [17]. Second, we found that older patients with a higher pulse rate were at greater risk of a primary reduction in OBF, and that this reduction preceded a decrease in circumpapillary RNFL thickness (cpRNFLT) in the superior and temporal quadrants [18]. These findings led us to theorize that different risk factors are associated with different pathophysiologicals and disc phenotypes, as well as different vulnerabilities to glucomatous lesions.

In the present study, we investigated how various measurable risk factors for glaucoma, including pre-treatment IOP (preIOP), CCT, oxidative stress, axial length (AL), systemic dBP, and MT, induced differing patterns of glucomatous structural damage. These risk factors were, in part, correlated to each other, so we divided the subjects into three groups based on high, middle, and low values of corrected parameters for each of the various risk factors (i.e., the total number of patients was divided into high, middle, and low preIOP groups, high, middle, and low CCT groups, etc.) and performed a multiple regression analysis to isolate the exact role of each risk factor. Then, we compared structural differences in glucomatous damage in the tripartite groups. These findings may help uncover new methods for the clinical management of glaucoma based on specific risk factors and allow the development of new treatments based on IOP-independent risk factors to address unmet medical needs.

**Materials and methods**

This study enrolled 458 eyes of 458 patients with open-angle glaucoma (OAG) (male/female: 244/214, age: 56.7 ± 14.4 years old, preIOP: 18.8 ± 7.0 mmHg, mean deviation: -8.9 ± 7.8 dB, cpRNFLT: 71.4 ± 17.5 μm; Table 1). The inclusion criteria were: (1) a diagnosis of OAG, including either primary open-angle glaucoma (POAG) or normal-tension glaucoma (NTG) and (2) a glucomatous visual field meeting the Anderson-Patella classification; i.e., with one or more of the following: (1) a cluster of three points with probabilities of < 5% on the pattern deviation map in at least one hemifield (including ≥ 1 point with probability of < 1% or a cluster of two points with a probability of < 1%), (2) glucomatous hemifield test results outside the normal limits or (3) a pattern standard deviation beyond 95% of normal limits, as confirmed in at least 2 reliable examinations. Preperimetric glucomatous patients were not included in this study. The exclusion criteria were: (1) age younger than 20 years, (2) best-corrected visual acuity (BCVA) less than 0.3, (3) high myopia (i.e., spherical equivalent refraction error < -7.0 diopters), and (4) the presence of non-OAG ocular disease or any other systemic disease affecting the visual field.

The baseline clinical parameters recorded for each patient were age, gender, and refractive error. IOP was measured with Goldman applanation tonometry at the time of the initial diagnosis of OAG, before the use of any medications for glaucoma (preIOP) or post-treatment IOP (postIOP). CCT was measured with anterior-segment OCT (Casia, Tomey Corporation, Nagoya, Japan). Mean deviation (MD) and pattern standard deviation (PSD) were measured with the Humphrey visual field analyzer (HFA) using the Swedish interactive threshold algorithm (SITA)-standard strategy of the 24–2 program. Only reliably measured data were used (i.e., with a fixation loss < 20%, false-negative errors < 15%, and false-negative errors < 33%). The LSFG-NAVI device (Softcare Co., Ltd., Fukutsu, Japan) was used to assess OBF in the ONH by measuring MT, a measurement parameter expressed in arbitrary units. MT does not represent global ocular hemodynamics, as it is only a single parameter captured over a few seconds. However, it has excellent reproducibility [19] and has been shown to be significantly correlated to microsphere-measured OBF in the posterior ciliary artery in primates [20], hydrogen
Table 1  Characteristics of glaucoma patients divided into three groups based on low, medium, or high corrected pre-treatment intraocular pressure

| Variable                        | Total (reference) (n = 458) | Low cIOP (n = 153) | Mid cIOP (n = 152) | High cIOP (n = 153) | P value | p value of pairwise comparison test |
|---------------------------------|-----------------------------|--------------------|--------------------|---------------------|---------|-----------------------------------|
|                                |                             |                    |                    |                     |         | Low—Mid                           |
|                                |                             |                    |                    |                     |         | Low—High                          |
|                                |                             |                    |                    |                     |         | Mid—High                          |
| cIOP (mmHg)                    | 18.8 ± 7.0                  | 13.4 ± 18          | 17.5 ± 13          | 25.6 ± 79           | 0.752   | 0.014                             |
| Male / female                  | 244 / 214                   | 78 / 75            | 84 / 68            | 82 / 71             |         | < 0.001 ***                       |
| CCT (µm)                       | 516.6 ± 33.7                | 514.3 ± 34.3       | 518.2 ± 33.0       | 517.2 ± 39.4        | 0.528   | 0.041                             |
| BAP (µmol/L)                   | 2127.3 ± 2849               | 2147.28 ± 236.0    | 2106.8 ± 353.9     | 2128.5 ± 253.0      | 0.902   | 0.014                             |
| AL (mm)                        | 25.4 ± 2.1                  | 25.7 ± 17          | 25.4 ± 17          | 25.4 ± 20           | 0.123   | 0.014                             |
| dIOP (mmHg)                    | 76.8 ± 13.6                 | 740.1 ± 12.1       | 765.4 ± 148        | 798.1 ± 134         | < 0.001 *** | 0.014                             |
| cMT (arbitrary units)          | 99.6 ± 26                   | 100.2 ± 28         | 101.2 ± 28         | 96.4 ± 24           | 0.149   | 0.001 ***                         |
| post IOP (mmHg)                | 148.4 ± 4.7                 | 130.4 ± 13         | 144.0 ± 32         | 171.5 ± 59          | < 0.001 *** | 0.014                             |
| Age (year)                     | 56.7 ± 14.4                 | 55.4 ± 15.4        | 56.2 ± 143         | 58.5 ± 133          | 0.106   | 0.001 **                         |
| MD (dB)                        | -8.9 ± 7.8                  | -6.7 ± 6.9         | -9.0 ± 7.4         | -11.1 ± 8.3         | < 0.001 *** | 0.010 *                          |
| PSD (dB)                       | 80.4 ± 4.4                  | 70.4 ± 3.4         | 85.2 ± 4.5         | 80.4 ± 41           | 0.004 ** | 0.025 *                          |
| Total cpRNFLT (µm)             | 71.4 ± 17.5                 | 75.8 ± 16.1        | 729.1 ± 167        | 658.1 ± 182         | < 0.001 *** | 0.046                             |
| Quadrant cpRNFLT (µm)          | 4.Temporal                  | 645.4 ± 205        | 691.1 ± 202        | 675.9 ± 203         | 0.591   | 0.001 ***                         |
|                                | 4.Superior                  | 856.4 ± 273        | 918.2 ± 27            | 865.7 ± 27           | 0.727   | 0.001 ***                         |
|                                | 4.Nasal                     | 580.0 ± 165        | 587.1 ± 15          | 583.1 ± 17          | 0.704   | 0.001 ***                         |
|                                | 4.Inferior                  | 776.2 ± 285        | 832.1 ± 28          | 791.7 ± 273         | 0.768   | 0.001 ***                         |
| 12-sector clockwise cpRNFLT (µm) | Temporal                  | 609.4 ± 267        | 649.3 ± 227         | 633.2 ± 227         | 0.545   | 0.001 ***                         |
|                                | 9 o’clock                  | 611.1 ± 192        | 642.2 ± 177         | 638.1 ± 186         | 0.554   | 0.001 ***                         |
|                                | 12 o’clock                 | 715.2 ± 286        | 782.8 ± 288         | 756.8 ± 280         | 0.609   | 0.001 ***                         |
|                                | 11 o’clock                 | 879.9 ± 394        | 994.0 ± 47          | 874.0 ± 401         | 0.770   | 0.001 ***                         |
|                                | 12 o’clock                 | 858.4 ± 315        | 903.2 ± 292         | 854.3 ± 312         | 0.817   | 0.001 ***                         |
|                                | 1 o’clock                  | 831.3 ± 273        | 855.8 ± 258         | 865.8 ± 287         | 0.774   | 0.001 ***                         |
|                                | 1 o’clock                  | 654.5 ± 220        | 656.2 ± 21          | 661.2 ± 224         | 0.646   | 0.001 ***                         |
|                                | 3 o’clock                  | 530.3 ± 175        | 539.1 ± 15          | 530.1 ± 197         | 0.519   | 0.001 ***                         |
|                                | 4 o’clock                  | 556.8 ± 175        | 567.6 ± 16          | 559.1 ± 173         | 0.543   | 0.001 ***                         |
|                                | 6 o’clock                  | 764.6 ± 246        | 795.2 ± 288         | 777.2 ± 230         | 0.731   | 0.001 ***                         |
|                                | 7 o’clock                  | 833.3 ± 358        | 893.4 ± 347         | 862.6 ± 369         | 0.743   | 0.001 ***                         |
| Disc topography                | Disc area                  | 206.0 ± 0.75       | 205.0 ± 0.75        | 203.0 ± 0.79        | 0.385   | 0.001 ***                         |
|                                | Cup area                   | 152.0 ± 0.78       | 147.0 ± 0.79        | 147.0 ± 0.79        | 1.628   | 0.033 *                          |
|                                | Rim area                   | 054.0 ± 0.42       | 058.0 ± 0.35        | 055.0 ± 0.34        | 0.047   | 0.001 ***                         |
|                                | Cup volume                 | 043.0 ± 0.36       | 039.0 ± 0.3         | 042.0 ± 0.34        | 0.050   | 0.001 *                          |
|                                | Rim volume                 | 005.0 ± 0.07       | 006.0 ± 0.05        | 005.0 ± 0.06        | 0.005   | 0.001 ***                         |
|                                | CD area ratio              | 072.0 ± 0.20       | 069.0 ± 0.19        | 070.0 ± 0.19        | 0.076   | 0.001 ***                         |
|                                | Linear CD ratio            | 084.0 ± 0.14       | 082.0 ± 0.14        | 083.0 ± 0.13        | 0.086   | 0.001 ***                         |
|                                | Vertical CD ratio          | 086.0 ± 0.15       | 086.4 ± 0.14        | 086.4 ± 0.15        | 0.089   | 0.001 ***                         |
|                                | Disc diameter (V)          | 166.0 ± 0.25       | 167.0 ± 0.24        | 166.0 ± 0.26        | 1.652   | 0.001 ***                         |
|                                | Disc diameter (09)         | 157.0 ± 0.31       | 156.0 ± 0.29        | 154.0 ± 0.31        | 1.590   | 0.001 ***                         |
Table 1 (continued)

| Variable                      | Total (reference) (n = 458) | Low cIOP (n = 153) | Mid cIOP (n = 152) | High cIOP (n = 153) | P value | p value of pairwise comparison test |
|-------------------------------|-----------------------------|-------------------|--------------------|---------------------|---------|------------------------------------|
|                               |                             |                   |                    |                     |         | Low—Mid  | Low—High | Mid—High |
| Macular GCC thickness (μm)    | 78.0 ± 14.7                 | 82.8 ± 13.6       | 81.3 ± 15.0        | 75.7 ± 14.6         | < 0.001 *** | 0.886    | < 0.001 *** | < 0.001 *** |
| Superior                      | 83.5 ± 17.0                 | 86.4 ± 15.9       | 85.8 ± 17.3        | 78.4 ± 16.7         | < 0.001 *** | 0.915    | < 0.001 *** | < 0.001 *** |
| Inferior                      | 76.5 ± 15.6                 | 79.2 ± 15.0       | 77.3 ± 16.4        | 72.9 ± 14.8         | < 0.001 *** | 0.549    | < 0.001 *** | 0.020 *   |

Asterisks: ** indicates p < 0.05, ***P < 0.01, and ****p < 0.001. Mid Middle, cIOP Corrected pre-treatment intraocular pressure, CCT Central corneal thickness, BAP Biological antioxidant potential, AL Axial length, dBP Dilated blood pressure, cMT Corrected mean blur rate in the tissue area of the optic nerve, postIOP Post-treatment IOP with applanation tonography, MD Mean deviation, measured with the Humphrey visual field analyzer, PSD Pattern standard deviation, C/D Cup-disc ratio
gas clearance–measured OBF, [21] and the severity of glaucomatous damage [22]. In this study, we used MT as a parameter to represent OBF. LSFG images were captured after subjects rested for 10 min in a dark room. Stable systolic and diastolic blood pressure were measured simultaneously with LSFG.

Swept-source OCT (DRI OCT Triton, Topcon Corp., Tokyo, Japan) was used for the assessment of structure. Horizontal disc scans and macular maps (6 × 6 mm, 512 A scans × 256 frames) were obtained and software was used (FastMap Ver. 10.16, Topcon) to identify the boundaries of the retinal nerve fiber layer (RNFL), ganglion cell layer and inner plexiform layer (GCIPL), and ganglion cell complex (GCC) layer. Total, quadrant, and clock-hours cpRNFL thickness and total and hemifield macular GCC thickness were used for the analysis.

We used multi-regression analysis to calculate a corrected MT (cMT) index by normalizing for three confounding factors: age, AL, and a weighted count of retinal ganglion cells (wRGC), as previously described [17]. Pre-IOP was corrected based on CCT (cIOP).

Blood samples were collected at least 3 h after the last meal and were immediately examined for oxidative stress with a free radical analyzer system (Free Carpe Diem, Wismerll Company Ltd., Tokyo, Japan), according to the manufacturer’s instructions, as previously described [23]. The level of diacron-reactive oxygen metabolites was expressed in U. Carr. and biological antioxidant potential (BAP) was expressed in µmol/L.

This study adhered to the tenets of the Declaration of Helsinki, and the protocols were approved by the Clinical Research Ethics Committee of the Tohoku University Graduate School of Medicine (study 2021-1-430).

Statistical analysis
This study used a comparison analysis, rather than a linear correlation analysis, for two reasons. First, some risk factors were correlated with each other. To compensate, cMT was corrected for age, AL, and wRGC, and cIOP was corrected for CCT in the multi-regression analysis. Second, some of the measurements we examined have already been reported to be risk factors for glaucoma at both low and high levels. Therefore, we divided the subjects into three equal groups based on their differing risk factors to assess differences in structural changes and local susceptibility to glaucomatous damage in the groups. This analysis used the Kruskal–Wallis test. If there was a significant difference among the subgroups, we performed pairwise comparisons with the Steel–Dwass test. The significance level was set at 5%. Since this study aimed to evaluate the association between each factor in an exploratory manner, multiplicity between groups was adjusted in the Steel–Dwass test, but multiplicity between tests was not considered. All statistical analyses were performed with JMP software (Pro version 16.1.0, SAS Institute Japan Inc., Tokyo, Japan) and R software (version 4.1.1, R Foundation, Vienna, Austria).

Results
We found a significant association between preIOP and CCT (r = 0.14, p = 0.005), which prompted us to calculate corrected preIOP (cIOP), which corrected for CCT, with a regression analysis. We also calculated corrected MT (cMT), which corrected for age, AL, CCT, and wRGC. We then divided the total group of patients into subgroups for low, middle, and high values of cIOP, CCT, AL, dBP, BAP, and cMT, and compared these three-part subgroups.

The cIOP subgroups differed significantly in dBP, postIOP, MD and PSD (Table 1). We found that dBP in the high cIOP group was significantly higher than the low and middle cIOP groups; PSD was significantly lower and MD was better in the low cIOP group than in the middle and high cIOP groups. The three subgroups had significantly different total, temporal, superior, and inferior cpRNFLT and cpRNFLT in the 1, 5, 6, 7, 8, 9, 10, 11, and 12 o’clock sectors. The high cIOP group had significantly lower temporal, superior, and inferior cpRNFLT and cpRNFLT in the 1, 5, 6, 8, 9, and 10 o’clock sectors. There were no differences in disc area or disc diameter, but in the high cIOP group, rim volume was smaller and the C/D area ratio was larger than in the low and middle cIOP groups. Total, superior, and inferior macular GCC thickness was significantly lower in the high cIOP group.

The CCT subgroups had significant differences in cIOP, postIOP and age, but similar MD (Table 2). The three subgroups had significantly different total and temporal cpRNFLT and cpRNFLT in the 8, 9, and 10 o’clock sectors. The high CCT group had significantly higher temporal cpRNFLT and cpRNFLT in the 8 and 10 o’clock sectors. There were also differences in cup volume in the three groups. Total and superior macular GCC thickness was significantly lower in the low CCT group than in the high CCT group.

The AL subgroups had significant differences in sex, dBP and age (Table 3). We found that dBP in the low AL group was significantly higher than in the middle and high AL groups. Age was significantly higher in the low AL group than in the middle and high AL groups. The three groups had significantly different temporal cpRNFLT and cpRNFLT in the 8, 9, and 10 o’clock sectors. The low AL group had significantly lower temporal cpRNFLT and cpRNFLT in the 8, 9, and 10 o’clock sectors. There were no differences in disc area, but in the low AL group, rim volume was smaller. Total and inferior macular GCC
thickness was significantly lower in the high AL group than in the middle AL group.

The dBP subgroups had significant differences in sex, cIOP, BAP, postIOP and MD (Table 4). PreIOP and postIOP in the high dBP group were significantly higher than in the low dBP group and BAP and MD were significantly lower than in the low dBP group. The three groups had significantly different total, superior and inferior cpRNFLT and cpRNFLT in the 6, 7, 10, 11, and 12 o’clock sectors. CpRNFLT in the superior and inferior quadrants and cpRNFLT in the 6, 10, 11 and 12 o’clock sectors were significantly lower in the high dBP group than in the low dBP group. There were no differences in disc area, cup volume, or disc diameter, but in the high dBP group, rim area and rim volume were smaller and the vertical C/D ratio was larger than in the low dBP group. Total, superior, and inferior macular GCC thickness was significantly lower in the high dBP group than in the low dBP group.

The BAP subgroups had significantly different sex and dBP (Table 5). We found that dBP in the low BAP group was significantly higher than the middle and high BAP groups. CpRNFLT in the 10 o’clock sector was significantly different in the three groups. There were no differences in disc topography or macular GCC thickness.

The cMT subgroups had significant differences in sex and postIOP (Table 6). PostIOP in the high cMT group was significantly higher than in the low and middle cMT groups. The three groups had significantly different total, temporal, superior, and inferior cpRNFLT and cpRNFLT in the 5, 8, 9 and 10 o’clock sectors. CpRNFLT in the 8, 9, and 10 o’clock sectors was significantly higher in the high cMT group. In the high cMT group, cup area, cup volume, linear C/D ratio, and vertical C/D ratio were smaller than in the low and middle cMT groups. Total, superior, and inferior macular GCC thickness was significantly higher in the high cMT group.

Discussion

Glaucoma is a multifactorial disease with a variety of reported risk factors. We previously showed that it was possible to adjust OBF measurements with a multiregression analysis and succeeded in creating an OBF index by adjusting for confounding factors [17]. Here, we expanded this approach to include five other risk factors with different data sets. No previous report has measured these risk factors quantitatively in the same cases. Here, we measured each risk factor in a hospital-based group of 458 glaucoma cases and investigated characteristics of the patients. For each of the risk factors, we performed an independent analysis that divided the patients into three groups based on whether the measured value was low, middle, or high. We then compared structural characteristics and susceptibility area among these groups. Our findings suggest that patients with specific risk factors have unique phenotypes, and that each risk factor is associated with specific types of damage, both in the macula and the optic disc. For example, the patients with high cIOP, low CCT, high AL, and high dBP had a greater loss of macular GCC thickness, which is associated with a lower quality of life. Furthermore, the patients with high cIOP, low CCT, high dBP, and low cMT had a greater total loss of cpRNFLT, and the patients with high cIOP, low AL, and low cMT had a larger C/D area ratio. Therefore, quantifying specific risk factors may help with the classification of specific glaucoma types and clarify the role that different disease mechanisms play in individual glaucoma patients, enabling the future development of IOP-independent treatments for glaucoma.

High IOP is an evidence-based risk factor for glaucoma and the sole modifiable risk factor in glaucoma treatment. In this study, HFA MD was significantly worse in the high cIOP group than the low cIOP group when these groups had similar age and peripapillary cpRNFLT damage in the temporal, superior, and inferior quadrants with large cupping. The direct pathophysiological effect of high IOP remains unclear. High IOP influences the curvature of the lamina cribrosa (LC) [24]. Deformation of the LC induces compression of the RGC axons and of the vessels, both in the optic nerve head and the chorioid [25]. In vitro findings show that cultivated astrocytes have a significant gene response to high pressure [26], but that cultivated RGCs do not, suggesting that high IOP induces RGC death via glia-neuronal interaction. Thus, high IOP simultaneously induces axonal damage and lowers OBF by causing deformation of the LC in patients with glaucoma, making high IOP a critical risk factor for glaucoma.

In this study, we found that glaucoma cases with low CCT had lower temporal cpRNFLT and had high CCT with a smaller cup volume. CCT is highly heritable, and low CCT is an independent risk factor for the progression of ocular hypertension to open-angle glaucoma [27]. However, whether low CCT has a negative effect in glaucoma-induced RGC death remains unclear. Previously, cases with low CCT have been found to have low IOP, as measured with Goldmann applanation tonometry [28], which influences the IOP-dependent degeneration pathway. Another hypothesis is that low CCT is related to low-strength collagen in the sclera, cornea, and LC. The strength of the sclera plays a critical role in IOP-induced deformation of the LC [29, 30], and patients with lower corneal deformation amplitude show greater LC depth, greater cup area, a deeper cup, and smaller peripapillary atrophy zone than those with higher corneal deformation amplitude [31]. Thus, a significant body of evidence
Table 2  Characteristics of glaucoma patients divided into three groups based on low, medium, or high CCT

| Variable                  | Total (reference) (n = 458) | Low CCT (n = 153) | Mid CCT (n = 152) | High CCT (n = 153) | P value | p value of pairwise comparison test |
|---------------------------|-----------------------------|-------------------|-------------------|-------------------|---------|-------------------------------------|
| CCT (μm)                  | 516.6 ± 35.7                | 479.8 ± 18.3      | 515.1 ± 8.2       | 554.5 ± 24.5      | 0.114   |                                     |
| Male / female             | 244 / 214                   | 76 / 77           | 76 / 76           | 92 / 61           | 0.006** | 0.144                               |
| dIOP (mmHg)               | 18.8 ± 7.0                  | 17.7 ± 5.9        | 19.4 ± 8.2        | 19.5 ± 6.6        | 0.006** | 0.004** 0.373                      |
| cIOP (mmHg)               | 2127.3 ± 284.9              | 2085.6 ± 304.7    | 2144.3 ± 273.3    | 2152.1 ± 273.6    | 0.071   |                                     |
| Male / female             | 244 / 214                   | 76 / 77           | 76 / 76           | 92 / 61           | 0.071   |                                     |
| dBP (mmHg)                | 76.8 ± 13.6                 | 77.3 ± 14.5       | 76.4 ± 13.5       | 76.5 ± 13.0       | 0.072   |                                     |
| cMT (arbitrary units)     | 9.9 ± 2.6                   | 9.6 ± 2.5          | 10.2 ± 2.8        | 10.1 ± 2.6        | 0.063   |                                     |
| Total cpRNFLT (μm)        | 71.4 ± 17.5                 | 68.9 ± 17.7       | 71.7 ± 17.9       | 73.8 ± 16.6       | 0.021*  | 0.321 0.014* 0.415                   |
| Quadrant cpRNFLT (μm)     |                             |                   |                   |                   |         |                                     |
| 4_Temporal               | 64.5 ± 20.5                 | 60.4 ± 18.1       | 63.4 ± 21.4       | 69.7 ± 21.0       | <0.001 *** | 0.506 <0.001 *** 0.040 *                      |
| 4_Superior               | 85.6 ± 27.3                 | 82.1 ± 27.9       | 87.4 ± 28.1       | 87.4 ± 25.7       | 0.166   |                                     |
| 4_Nasal                  | 58.0 ± 16.5                 | 57.2 ± 17.2       | 58.5 ± 16.0       | 58.3 ± 16.4       | 0.801   |                                     |
| 4_Inferior               | 77.6 ± 28.5                 | 75.7 ± 28.7       | 77.4 ± 28.7       | 79.7 ± 28.1       | 0.334   |                                     |
| 12-sector clockwise cpRNFLT (μm) |                   |                   |                   |                   |         |                                     |
| Temporal                 |                             |                   |                   |                   |         |                                     |
| 8 o'clock                | 60.9 ± 24.7                 | 57.6 ± 19.9       | 59.3 ± 29.3       | 65.6 ± 23.4       | 0.002** | 0.941 0.004** 0.016*                   |
| 9 o'clock                | 61.1 ± 19.2                 | 57.3 ± 15.4       | 61.5 ± 22.7       | 64.6 ± 18.1       | 0.002** | 0.319 <0.001 *** 0.125               |
| 10 o'clock               | 71.5 ± 28.6                 | 66.1 ± 26.8       | 69.6 ± 28.3       | 78.9 ± 29.2       | <0.001 *** | 0.601 <0.001 *** 0.005**             |
| Superior                 |                             |                   |                   |                   |         |                                     |
| 11 o'clock               | 87.9 ± 39.4                 | 82.9 ± 38.2       | 87.7 ± 39.8       | 93.0 ± 39.6       | 0.080   |                                     |
| 12 o'clock               | 85.8 ± 31.5                 | 82.8 ± 31.8       | 88.5 ± 32.2       | 96.7 ± 30.4       | 0.216   |                                     |
| 1 o'clock                | 83.1 ± 27.3                 | 81.1 ± 28.6       | 85.8 ± 27.8       | 82.5 ± 25.2       | 0.377   |                                     |
| Nasal                    |                             |                   |                   |                   |         |                                     |
| 2 o'clock                | 65.4 ± 22.0                 | 64.3 ± 23.8       | 66.7 ± 21.9       | 65.4 ± 20.3       | 0.718   |                                     |
| 3 o'clock                | 53.0 ± 17.5                 | 52.1 ± 16.4       | 52.3 ± 14.5       | 54.0 ± 20.8       | 0.441   |                                     |
| 4 o'clock                | 55.6 ± 17.5                 | 55.3 ± 17.5       | 56.6 ± 17.7       | 55.0 ± 17.5       | 0.828   |                                     |
| Inferior                 |                             |                   |                   |                   |         |                                     |
| 5 o'clock                | 76.4 ± 24.6                 | 75.4 ± 26.7       | 77.8 ± 23.8       | 76.9 ± 23.2       | 0.713   |                                     |
| 6 o'clock                | 83.3 ± 35.8                 | 80.8 ± 36.3       | 83.7 ± 35.5       | 85.4 ± 35.6       | 0.460   |                                     |
| 7 o'clock                | 73.1 ± 39.7                 | 70.8 ± 37.9       | 70.8 ± 39.8       | 77.7 ± 41.0       | 0.222   |                                     |
Table 2 (continued)

| Variable                  | Total (reference) (n = 458) | Low CCT (n = 153) | Mid CCT (n = 152) | High CCT (n = 153) | P value | p value of pairwise comparison test |
|---------------------------|-----------------------------|-------------------|-------------------|--------------------|---------|-----------------------------------|
|                           |                             |                    |                   |                    |         | Low—Mid | Low—High | Mid—High |
| Disc topography           |                             |                    |                   |                    |         |         |          |          |
| Disc area                 | 2.06 ± 0.75                 | 2.07 ± 0.87        | 2.13 ± 0.80       | 1.97 ± 0.56        | 0.423   |          |          |          |
| Cup area                  | 1.52 ± 0.78                 | 1.53 ± 0.83        | 1.62 ± 0.85       | 1.41 ± 0.65        | 0.154   |          |          |          |
| Rim area                  | 0.54 ± 0.42                 | 0.54 ± 0.48        | 0.51 ± 0.44       | 0.55 ± 0.33        | 0.100   |          |          |          |
| Cup volume                | 0.43 ± 0.36                 | 0.43 ± 0.35        | 0.50 ± 0.44       | 0.37 ± 0.27        | 0.018 * | 0.174   | 0.587    | 0.013 *  |
| Rim volume                | 0.05 ± 0.07                 | 0.05 ± 0.06        | 0.05 ± 0.09       | 0.05 ± 0.05        | 0.087   |          |          |          |
| C/D area ratio            | 0.72 ± 0.20                 | 0.72 ± 0.21        | 0.74 ± 0.20       | 0.69 ± 0.20        | 0.059   |          |          |          |
| Linear C/D ratio          | 0.84 ± 0.14                 | 0.84 ± 0.14        | 0.85 ± 0.14       | 0.82 ± 0.13        | 0.062   |          |          |          |
| Vertical C/D ratio        | 0.86 ± 0.15                 | 0.87 ± 0.14        | 0.87 ± 0.15       | 0.85 ± 0.15        | 0.457   |          |          |          |
| Disc diameter (V)         | 1.66 ± 0.25                 | 1.66 ± 0.28        | 1.68 ± 0.26       | 1.63 ± 0.22        | 0.440   |          |          |          |
| Disc diameter (H)         | 1.57 ± 0.31                 | 1.57 ± 0.35        | 1.60 ± 0.31       | 1.53 ± 0.25        | 0.393   |          |          |          |
| Macular GCC thickness (μm)| Total                       | 78.3 ± 13.6        | 79.4 ± 13.9       | 82.2 ± 16.3        | 0.032 * | 0.646   | 0.028 *  | 0.202    |
|                           | Superior                    | 83.5 ± 17.0        | 83.0 ± 16.6       | 86.1 ± 18.3        | 0.027 * | 0.632   | 0.022 *  | 0.198    |
|                           | Inferior                    | 76.5 ± 15.6        | 75.3 ± 14.7       | 75.7 ± 15.0        | 0.157   |          |          |          |

Arterisks: *** indicates p < 0.05, **** p < 0.01, and ***** p < 0.001. Mid Middle, cIOP Corrected pre-treatment intraocular pressure, CCT Central corneal thickness, BAP Biological antioxidant potential, AL Axial length, dBP Dilated blood pressure, cMT Corrected mean blur rate in the tissue area of the optic nerve, postIOP Post-treatment IOP with applanation tonography, MD Mean deviation, measured with the Humphrey visual field analyzer, PSD Pattern standard deviation, C/D Cup-disc ratio.
## Table 3  Characteristics of glaucoma patients divided into three groups based on low, medium, or high AL

| Variable          | Total (reference) \( (n = 458) \) | Low AL \( (n = 153) \) | Mid AL \( (n = 152) \) | High AL \( (n = 153) \) | \( p \) value | \( p \) value of pairwise comparison test |
|-------------------|-----------------------------------|------------------------|------------------------|------------------------|-------------|----------------------------------------|
| AL (mm)           | 25.4 ± 2.1                        | 23.5 ± 0.7            | 25.4 ± 0.6            | 27.5 ± 1.1            | 0.004 **    | Low—Mid  Low—High  Mid—High            |
| Male / female     | 244 / 214                         | 66 / 87               | 83 / 69               | 95 / 58               |             |                                        |
| cIOP (mmHg)       | 18.8 ± 7.0                        | 19.4 ± 7.1            | 18.9 ± 7.4            | 18.2 ± 6.4            | 0.340       |                                        |
| CCT (μm)          | 5166 ± 35.7                       | 5140 ± 38.0           | 5174 ± 34.6           | 5183 ± 34.4           | 0.158       |                                        |
| BAP (µmol/L)      | 2127.3 ± 284.9                    | 2131.2 ± 327.4       | 2148.5 ± 210.5        | 2102.6 ± 303.3        | 0.548       |                                        |
| dBp (mmHg)        | 76.8 ± 13.6                       | 76.1 ± 15.1           | 74.8 ± 12.7           | 79.4 ± 12.7           | 0.007 **    | 0.824  0.046 *  0.008 **               |
| cMT (arbitrary units) | 9.9 ± 2.6                        | 10.0 ± 2.5            | 9.9 ± 2.6             | 9.9 ± 2.8             | 0.825       |                                        |
| Age (years)       | 56.7 ± 14.4                       | 63.6 ± 14.0           | 55.5 ± 13.8           | 51.0 ± 12.5           | <0.001 ***  | <0.001 ***  <0.001 ***  0.002 **     |
| PSO (dB)          | -8.9 ± 7.8                        | -9.7 ± 8.3            | -8.2 ± 7.7            | -8.9 ± 7.3            | 0.208       |                                        |
| PsO (dB)          | 148 ± 4.7                         | 155 ± 50              | 148 ± 48              | 143 ± 42              | 1.14        |                                        |
| CIOP (mmHg)       | 24.8 ± 17.5                       | 69.8 ± 17.3           | 73.4 ± 176            | 71.2 ± 17.5           | 0.257       |                                        |
| Quadrant cpRNFLT (μm) | 64.5 ± 20.5                       | 58.3 ± 14.5           | 67.3 ± 22.4           | 67.8 ± 22.5           | <0.001 ***  | <0.001 ***  <0.001 ***  0.927       |
| Superior          | 86.5 ± 27.3                       | 86.4 ± 26.4           | 87.6 ± 27.1           | 82.9 ± 28.3           | 0.312       |                                        |
| Nasal             | 580 ± 16.5                        | 574 ± 14.6            | 576 ± 15.0            | 590 ± 19.5            | 0.466       |                                        |
| Inferior          | 776 ± 28.5                        | 772 ± 29.8            | 809 ± 27.9            | 748 ± 27.6            | 0.159       |                                        |
| 12-sector clockwisecpRNFLT (μm) | 60.9 ± 24.7                       | 55.0 ± 16.3           | 65.3 ± 29.7           | 62.4 ± 25.1           | 0.003 **    | 0.032 *  0.002 **  0.843              |
| Temporal          | 61.1 ± 19.2                       | 55.3 ± 12.3           | 62.7 ± 18.9           | 65.4 ± 23.2           | <0.001 ***  | <0.001 ***  <0.001 ***  0.668       |
| 10 o'clock        | 71.5 ± 28.6                       | 64.7 ± 21.9           | 740 ± 29.7            | 738 ± 32.07           | 0.006 **    | 0.029 *  0.009 **  0.943              |
| Superior          | 87.9 ± 39.4                       | 86.2 ± 35.5           | 93.8 ± 41.3           | 83.87 ± 40.7          | 0.107       |                                        |
| Nasal             | 85.8 ± 31.5                       | 89.5 ± 32.2           | 861 ± 29.5            | 81.8 ± 32.4           | 0.120       |                                        |
| Inferior          | 83.1 ± 27.3                       | 83.5 ± 25.2           | 828 ± 25.9            | 83.1 ± 30.5           | 0.976       |                                        |
| Ocular            | 65.4 ± 22.0                       | 67.2 ± 20.2           | 647 ± 21.6            | 645 ± 24.1            | 0.637       |                                        |
| Superior          | 530 ± 17.5                        | 507 ± 14.6            | 522 ± 13.7            | 559 ± 22.4            | 0.077       |                                        |
| Nasal             | 556 ± 17.5                        | 54.4 ± 15.0           | 559 ± 16.3            | 566 ± 20.7            | 0.586       |                                        |
| Inferior          | 76.4 ± 246                        | 77.0 ± 249            | 768 ± 237             | 75.4 ± 25.2           | 0.920       |                                        |
| 7 o'clock         | 83.3 ± 35.8                       | 83.1 ± 37.4           | 881 ± 35.5            | 788 ± 33.9            | 0.079       |                                        |
| 7 o'clock         | 73.1 ± 39.7                       | 71.5 ± 39.5           | 778 ± 40.9            | 70.1 ± 38.5           | 0.086       |                                        |
| Variable                        | Total (reference) (n = 458) | Low AL (n = 153) | Mid AL (n = 152) | High AL (n = 153) | P value | p value of pairwise comparison test |
|--------------------------------|------------------------------|------------------|------------------|-------------------|---------|-----------------------------------|
|                                |                              |                  |                  |                   |         | Low—Mid  Low—High Mid—High        |
| Disc topography                |                              |                  |                  |                   |         |                                  |
| Disc area                      | 2.06 ± 0.75                  | 1.96 ± 0.48      | 2.00 ± 0.61      | 2.21 ± 1.03       | 0.286   |                                   |
| Cup area                        | 1.52 ± 0.78                  | 1.51 ± 0.59      | 1.41 ± 0.62      | 1.65 ± 1.04       | 0.174   |                                   |
| Rim area                        | 0.54 ± 0.42                  | 0.45 ± 0.33      | 0.60 ± 0.48      | 0.56 ± 0.43       | 0.006 **| 0.006 ** 0.062 0.709             |
| Cup volume                      | 0.43 ± 0.36                  | 0.45 ± 0.30      | 0.42 ± 0.34      | 0.44 ± 0.44       | 0.112   |                                   |
| Rim volume                      | 0.05 ± 0.07                  | 0.04 ± 0.05      | 0.06 ± 0.08      | 0.06 ± 0.06       | <0.001 ***| 0.002 ** 0.008 ** 0.865        |
| C/D area ratio                  | 0.72 ± 0.20                  | 0.76 ± 0.19      | 0.69 ± 0.20      | 0.71 ± 0.21       | 0.008 **| 0.007 ** 0.088 0.681            |
| Linear C/D ratio                | 0.84 ± 0.14                  | 0.86 ± 0.14      | 0.82 ± 0.13      | 0.83 ± 0.15       | 0.008 **| 0.006 ** 0.093 0.661           |
| Vertical C/D ratio              | 0.86 ± 0.15                  | 0.88 ± 0.14      | 0.85 ± 0.14      | 0.86 ± 0.16       | 0.022 * | 0.019 * 0.742 0.132            |
| Disc diameter (V)               | 1.66 ± 0.25                  | 1.62 ± 0.18      | 1.64 ± 0.21      | 1.71 ± 0.34       | 0.025 * | 0.992 0.036 * 0.071             |
| Disc diameter (H)               | 1.57 ± 0.31                  | 1.53 ± 0.21      | 1.55 ± 0.27      | 1.61 ± 0.40       | 0.351   |                                   |
| Macular GCC thickness (μm)      |                              |                  |                  |                   |         |                                  |
| Total                           | 78.0 ± 14.7                  | 80.3 ± 13.8      | 82.3 ± 14.3      | 77.3 ± 15.6       | 0.049 * | 0.604 0.303 0.039 *              |
| Superior                        | 83.5 ± 17.0                  | 84.5 ± 15.7      | 85.5 ± 16.8      | 80.6 ± 18.2       | 0.119   |                                   |
| Inferior                        | 76.5 ± 15.6                  | 76.2 ± 15.8      | 79.1 ± 15.1      | 74.1 ± 15.6       | 0.017 * | 0.211 0.471 0.013 *              |

Asterisks: ** indicates p < 0.05, ***p < 0.01, and ****p < 0.001. Mid Middle, cIOP Corrected pre-treatment intraocular pressure, CCT Central corneal thickness, BAP Biological antioxidant potential, AL Axial length, dBP Dilated blood pressure, cMT Corrected mean blur rate in the tissue area of the optic nerve, postIOP Post-treatment IOP with applanation tonography, MD Mean deviation, measured with the Humphrey visual field analyzer, PSD Pattern standard deviation, C/D Cup-disc ratio
suggests that properties of the cornea affect the situation of the optic nerve head and influence a patient’s vulnerability to glaucomatous changes.

Myopia has been described as an evidence-based risk factor for glaucoma [6]. Patients with higher myopia have been reported to be more likely to have OAG (OR, 1.59, 95% CI, 1.33–1.91; OR, 2.92, 95% CI, 1.89–4.52 for low, moderate, and high myopia, respectively) [32]. Even though a tilted optic disc has been found to have no statistically significant association with glaucoma progression, greater optic disc torsion is associated with reduced glaucoma deterioration risk, as assessed by functional progression [33]. The prevalence of myopia is higher in East Asia [34], and because NTG is the most common subtype of OAG in Asia [35] there may be an ethnic bias. Elongated AL induces low OBF [22], lamina defects [36], and thinning of the LC [37]. Furthermore, elongated AL induces enlargement of the peripapillary atrophy zone, which results in damage to central visual function [38]. In this study, macular GCC was thinner in glaucoma cases with high AL than in those with middle AL. Interestingly, we found that temporal cpRNFLT was also lower in cases with low AL than in normal subjects. Cases with low AL were significantly older and had higher dBP in the three groups, while patients with POAG and low AL had higher 24-h IOP fluctuation [39] than patients with myopia. These characteristics increase vulnerability to change in temporal cpRNFLT, but the precise reason for this is still unclear. Further research is needed to clarify the mechanism of macular damage in eyes with a short AL.

We found that the high systemic dBP group was more likely to have severe visual field defects, low total, superior, and inferior cpRNFLT, and low macular GCC thickness than the low dBP group. The group of patients with high dBP was significantly older with significantly lower BAP, suggesting that high dBP is related to systemic anti-oxidant levels. We also found that cIOP was high in the high dBP group. Thus, high dBP was related to older age and high IOP, resulting in more severe glaucoma. Previously, both low and high systemic blood pressure have been reported to be related to low OBF and the presence of glaucoma [12], while lower mean systemic blood pressure has been shown to be a risk factor for a smaller rim area in the superior optic disc [40]. Population-based epidemiological studies have found a strong relationship between low ocular perfusion pressure and OAG prevalence, incidence, and progression [5]. Subjects with Flammer syndrome, a type of primary vascular dysregulation, tend to have increased risk for NTG and a higher prevalence of optic disc hemorrhages [41]. Moreover, a study of nocturnal blood pressure changes found that subjects who were non-dippers or extreme dippers were at risk for progressive visual field loss in glaucoma [42]. These findings suggest that abnormalities in systemic BP, both high and low BP, are a risk factor for glaucoma, and point to the importance of measuring systemic BP in daily clinical practice. Furthermore, we need to conduct a study that includes the continuous measurement of systemic BP in order to determine the relationship between fluctuations in systemic BP and glaucoma progression.

The critical contribution of oxidative stress to glaucomatous damage has been previously described [1]. The total antioxidant status of the blood has been shown to be lower in OAG patients than control subjects [43]. Furthermore, younger male glaucoma cases with low antioxidant levels tend to have worse visual field defects [23]. In this study, there were more male glaucoma patients in the low BAP group. Oxidative stress has also previously been shown to be related to dysfunctions of the capillaries in the optic nerve head [44] and cases with low BAP have been shown to have higher dBP. Among structural changes, the loss of cpRNFLT was only detected in the 10 o’clock area; the cause of this vulnerability to oxidative stress remains unclear. Antioxidant treatments, such as a diet high in nitrates and green leafy vegetables, is associated with a lower POAG risk, particularly POAG with early paracentral VF loss at diagnosis [45]. A total of 33 interventional trials suggest that flavonoids exert a beneficial effect in glaucoma [46]. Thus, we developed several solutions based on these findings, such as dietary supplementation and boosted vegetable intake. We have also demonstrated that hesperidin has an antioxidant property in both mice [47] and humans [48].

Previously, we examined 533 patients with glaucoma and found that patients with low OBF were characterized by a larger cup-disc ratio and higher susceptibility to damage in the temporal disc and the macula area [17]. In this study, we found that cases with high OBF had higher total cpRNFLT, temporal and superior cpRNFLT, and macular GCC thickness. Previously, NTG eyes that were undergoing medical treatment and had greater 24-h mean ocular perfusion pressure fluctuations have been shown to have faster central visual field defect progression [49]. The blood supply of the optic nerve originates in a branch of the post ciliary artery and the circle of Zinn-Haller [50, 51]. Therefore, disturbances in these vessels may play a causative role in glaucomatous optic neuropathy. LSFG enables us to measure the deep layers of the optic nerve head around the LC [20]. Recently, we showed that reduced LSFG-measured tissue blood flow in the ONH was already detectible in PPG [14, 15] and that low OBF could predict the progression of glaucoma [16]. We have also clearly shown, with retrospective and prospective data, that low OBF is a predictor of temporal
| Variable                          | Total (reference) (n = 458) | Low dBP (n = 153) | Mid dBP (n = 152) | High dBP (n = 153) | \( P \) value | \( p \) value of pairwise comparison test |
|----------------------------------|-----------------------------|-------------------|-------------------|-------------------|-------------|------------------------------------------|
|                                 |                             | Low—Mid           | Low—High          | Mid—High          |             | Low—Mid—High                             |
| dBP (mmHg)                       | 76.8 ± 13.6                 | 62.9 ± 6.4        | 75.9 ± 2.9        | 91.4 ± 10.0       | 0.012 *     |                                          |
| Male / female                    | 244 / 214                   | 67 / 86           | 85 / 67           | 92 / 61           | 0.001 ***   | 0.075                                    | 0.001 *** 0.193 |
| cIOP (mmHg)                      | 18.8 ± 7.0                  | 17.4 ± 5.3        | 18.7 ± 6.4        | 20.4 ± 8.4        | < 0.001 *** | 0.075                                    | 0.001 *** 0.193 |
| CCT (µm)                         | 516.6 ± 35.7                | 518.1 ± 33.9      | 518.0 ± 38.9      | 513.7 ± 34.2      | 0.418       |                                          |
| BAP (µmol/L)                     | 2127.3 ± 284.9              | 2170.9 ± 251.3    | 2153.1 ± 195.1    | 2088.7 ± 368.2    | 0.027 *     | 0.507                                    | 0.024 * 0.225 |
| AL (mm)                          | 25.4 ± 2.1                  | 25.2 ± 1.6        | 25.5 ± 1.8        | 25.7 ± 2.0        | 0.082       |                                          |
| cMT (arbitrary units)            | 9.9 ± 2.6                   | 10.0 ± 2.7        | 10.2 ± 2.6        | 9.7 ± 2.6         | 0.327       |                                          |
| postIOP (mmHg)                   | 14.8 ± 4.7                  | 13.9 ± 3.7        | 14.8 ± 4.7        | 15.8 ± 5.3        | < 0.001 *** | 0.227                                    | < 0.001 *** 0.103 |
| Age (years)                      | 56.7 ± 14.4                 | 54.3 ± 17.0       | 56.8 ± 13.5       | 58.9 ± 11.9       | 0.046 *     | 0.485                                    | 0.043 * 0.313 |
| MD (dB)                          | -8.9 ± 7.8                  | -7.5 ± 7.0        | -8.8 ± 7.6        | -10.5 ± 8.3       | 0.006 **    | 0.358                                    | 0.004 ** 0.166 |
| PSD (dB)                         | 8.0 ± 4.4                   | 7.4 ± 4.2         | 8.0 ± 4.6         | 8.6 ± 4.3         | 0.051       |                                          |
| Total cpRNFLT (µm)               | 71.4 ± 17.5                 | 73.7 ± 16.8       | 72.1 ± 18.1       | 68.6 ± 17.3       | 0.049 *     | 0.449                                    | 0.038 * 0.427 |
| Quadrant cpRNFLT (µm)            |                             |                   |                   |                   |             |                                          |
| 4_Temporal                       | 64.5 ± 20.5                 | 66.7 ± 21.0       | 65.1 ± 19.3       | 61.7 ± 21.1       | 0.060       |                                          |
| 4_Superior                       | 85.6 ± 27.3                 | 90.0 ± 26.4       | 85.1 ± 27.6       | 81.8 ± 27.5       | 0.026 *     | 0.229                                    | 0.022 * 0.516 |
| 4_Nasal                          | 58.0 ± 16.5                 | 57.7 ± 15.5       | 58.2 ± 16.7       | 58.0 ± 17.4       | 1.000       |                                          |
| 4_Inferior                       | 77.6 ± 28.5                 | 80.3 ± 28.4       | 80.1 ± 30.7       | 72.5 ± 25.7       | 0.033 *     | 0.842                                    | 0.034 * 0.134 |
| 12-sector clockwisecpRNFLT (µm)  |                             |                   |                   |                   |             |                                          |
| Temporal                         | 60.9 ± 24.7                 | 62.3 ± 24.4       | 62.0 ± 21.2       | 58.4 ± 27.8       | 0.124       |                                          |
| 9 o'clock                        | 61.1 ± 19.2                 | 62.2 ± 18.8       | 61.2 ± 20.4       | 60.1 ± 18.3       | 0.388       |                                          |
| 10 o'clock                       | 71.5 ± 28.6                 | 75.5 ± 29.1       | 72.5 ± 28.5       | 66.7 ± 27.6       | 0.017 *     | 0.676                                    | 0.019 * 0.097 |
| Superior                         | 87.9 ± 39.4                 | 94.5 ± 40.1       | 86.9 ± 40.1       | 82.3 ± 37.1       | 0.036 *     | 0.257                                    | 0.029 * 0.998 |
| 11 o'clock                       | 85.8 ± 31.5                 | 90.0 ± 31.3       | 85.7 ± 30.3       | 81.6 ± 32.4       | 0.021 *     | 0.435                                    | 0.019 * 0.212 |
| 12 o'clock                       | 83.1 ± 27.3                 | 85.5 ± 27.4       | 82.7 ± 26.4       | 81.3 ± 27.9       | 0.409       |                                          |
| Nasal                            | 65.4 ± 22.0                 | 65.5 ± 21.3       | 64.8 ± 21.9       | 66.0 ± 22.9       | 0.903       |                                          |
| 2 o'clock                        | 53.0 ± 17.5                 | 51.9 ± 14.4       | 54.2 ± 20.2       | 52.8 ± 17.3       | 0.784       |                                          |
| 3 o'clock                        | 55.6 ± 17.5                 | 55.8 ± 16.2       | 55.7 ± 18.1       | 55.4 ± 18.3       | 0.922       |                                          |
| 4 o'clock                        | 76.4 ± 24.6                 | 78.2 ± 24.7       | 77.0 ± 25.4       | 74.0 ± 23.6       | 0.252       |                                          |
| 5 o'clock                        | 83.3 ± 35.8                 | 86.1 ± 34.4       | 86.2 ± 38.0       | 77.6 ± 34.4       | 0.048 *     | 0.899                                    | 0.043 * 0.177 |
| 6 o'clock                        | 73.1 ± 39.7                 | 76.6 ± 42.3       | 77.1 ± 40.7       | 65.8 ± 34.9       | 0.027 *     | 0.987                                    | 0.064 * 0.044 * |
| Variable                      | Total (reference) (n = 458) | Low dBP (n = 153) | Mid dBP (n = 152) | High dBP (n = 153) | P value | p value of pairwise comparison test |
|-------------------------------|-----------------------------|-------------------|-------------------|-------------------|---------|-----------------------------------|
|                               |                             | Low—Mid | Low—High | Mid—High     |         |                                   |
| Disc topography               |                             |          |          |              |         |                                   |
| Disc area                     | 2.06 ± 0.75                 | 2.10 ± 0.67 | 2.02 ± 0.69 | 2.09 ± 0.80     | 0.894   |                                   |
| Cup area                      | 1.52 ± 0.78                 | 1.50 ± 0.73 | 1.48 ± 0.81 | 1.58 ± 0.81     | 0.461   |                                   |
| Rim area                      | 0.54 ± 0.42                 | 0.55 ± 0.34 | 0.54 ± 0.37 | 0.51 ± 0.52     | 0.032 * | 0.819 | 0.029 * | 0.154 |
| Cup volume                    | 0.43 ± 0.36                 | 0.42 ± 0.32 | 0.42 ± 0.40 | 0.46 ± 0.36     | 0.476   |                                   |
| Rim volume                    | 0.05 ± 0.07                 | 0.05 ± 0.05 | 0.05 ± 0.06 | 0.05 ± 0.09     | 0.046 * | 0.878 | 0.041 * | 0.176 |
| C/D area ratio                | 0.72 ± 0.20                 | 0.71 ± 0.19 | 0.71 ± 0.21 | 0.74 ± 0.21     | 0.076   |                                   |
| Linear C/D ratio              | 0.84 ± 0.14                 | 0.83 ± 0.13 | 0.83 ± 0.15 | 0.85 ± 0.14     | 0.074   |                                   |
| Vertical C/D ratio            | 0.86 ± 0.15                 | 0.85 ± 0.13 | 0.85 ± 0.16 | 0.88 ± 0.14     | 0.037 * | 0.757 | 0.030 * | 0.197 |
| Disc diameter (V)             | 1.66 ± 0.25                 | 1.66 ± 0.24 | 1.65 ± 0.24 | 1.67 ± 0.29     | 0.861   |                                   |
| Disc diameter (H)             | 1.57 ± 0.31                 | 1.58 ± 0.30 | 1.55 ± 0.28 | 1.57 ± 0.34     | 0.750   |                                   |
| Macular GCC thickness (μm)    |                             |          |          |              |         |                                   |
| Total                         | 78.0 ± 14.7                 | 82.2 ± 14.7 | 81.4 ± 14.4 | 76.3 ± 14.5     | 0.004 **| 0.585 | 0.003 ** | 0.060 |
| Superior                      | 83.5 ± 17.0                 | 86.4 ± 16.8 | 84.5 ± 16.6 | 79.6 ± 17.0     | 0.002 **| 0.400 | 0.001 ** | 0.077 |
| Inferior                      | 76.5 ± 15.6                 | 78.1 ± 16.0 | 78.3 ± 15.3 | 73.1 ± 15.12    | 0.016 * | 0.997 | 0.031 * | 0.037 * |

Asterisks: ** indicates *p < 0.05, ***p < 0.01, and ****p < 0.001. Mid Middle, cIOP Corrected pre-treatment intraocular pressure, CCT Central corneal thickness, BAP Biological antioxidant potential, AL Axial length, dBP Dilated blood pressure, cMT Corrected mean blur rate in the tissue area of the optic nerve, postIOP Post-treatment IOP with applanation tonography, MD Mean deviation, measured with the Humphrey visual field analyzer, PSD Pattern standard deviation, C/D Cup-disc ratio.
Table 5  Characteristics of glaucoma patients divided into three groups based on low, medium, or high BAP

| Variable                | Total (reference) (n = 458) | Low BAP (n = 153) | Mid BAP (n = 152) | High BAP (n = 153) | Pvalue   |
|-------------------------|-----------------------------|-------------------|-------------------|-------------------|----------|
|                         |                             | Low—Mid | Low—High | Mid—High |                       |
| BAP (µmol/L)            | 2127.3 ± 284.9              | 1849.3 ± 304.2   | 2159.2 ± 46.8     | 2372.2 ± 101.3    |          |
| Male / female           | 244 / 214                   | 97 / 56         | 71 / 81           | 76 / 77           | 0.008 ** |
| cIOP (mmHg)             | 18.8 ± 0.7                  | 19.0 ± 7.3       | 21.5 ± 34.3       | 21.8 ± 34.8       | 0.114    |
| AL (mm)                 | 25.4 ± 2.1                  | 25.7 ± 1.9       | 25.3 ± 1.7        | 25.4 ± 1.8        | 0.281    |
| dB (mmHg)               | 76.8 ± 13.6                 | 80.0 ± 15.2      | 76.0 ± 12.3       | 74.3 ± 12.8       | 0.003 ** |
| cMT (arbitrary units)   | 9.9 ± 2.6                   | 9.6 ± 2.5        | 10.2 ± 2.6        | 10.0 ± 2.7        | 0.226    |
| postIOP (mmHg)          | 148 ± 47                    | 148 ± 46         | 148 ± 45          | 148 ± 45          | 0.811    |
| Age (years)             | 56.7 ± 14.4                 | 58.3 ± 12.8      | 57.1 ± 13.1       | 54.8 ± 16.8       | 0.371    |
| MD (dB)                 | -8.9 ± 7.8                  | -9.4 ± 7.7       | -8.0 ± 7.3        | -9.4 ± 8.2        | 0.186    |
| PSD (dB)                | 8.0 ± 4.4                   | 8.3 ± 4.4        | 7.6 ± 4.6         | 8.2 ± 4.3         | 0.490    |
| Total cpRNFLT (µm)      | 71.4 ± 17.5                 | 70.2 ± 16.8      | 72.8 ± 17.8       | 71.3 ± 17.9       | 0.328    |
| Quadrant cpRNFLT (µm)   |                             |                   |                   |                   |          |
| Temporal                | 64.5 ± 20.5                 | 62.1 ± 20.1      | 66.3 ± 20.8       | 65.1 ± 20.7       | 0.149    |
| Superior                | 85.6 ± 27.3                 | 82.6 ± 26.3      | 87.1 ± 27.6       | 87.2 ± 27.9       | 0.165    |
| Nasal                   | 58.0 ± 16.5                 | 58.5 ± 16.4      | 58.3 ± 15.9       | 57.2 ± 17.3       | 0.578    |
| Inferior                | 77.6 ± 28.5                 | 77.2 ± 27.4      | 79.7 ± 28.6       | 75.9 ± 29.5       | 0.379    |
| 12-sector clockwisecpRNFLT (µm) |                 |                   |                   |                   |          |
| Temporal                |                             |                   |                   |                   |          |
| 8 o'clock               | 60.9 ± 24.7                 | 61.0 ± 27.4      | 62.5 ± 24.0       | 59.1 ± 22.4       | 0.584    |
| 9 o'clock               | 61.1 ± 19.2                 | 58.8 ± 16.7      | 62.6 ± 18.6       | 62.0 ± 21.8       | 0.291    |
| 10 o'clock              | 71.5 ± 28.6                 | 66.6 ± 27.0      | 73.8 ± 27.6       | 74.2 ± 30.6       | 0.042 ** |
| Superior                |                             |                   |                   |                   |          |
| 11 o'clock              | 87.9 ± 39.4                 | 82.2 ± 36.3      | 90.1 ± 40.4       | 91.4 ± 40.9       | 0.097    |
| 12 o'clock              | 85.8 ± 31.5                 | 82.6 ± 30.8      | 87.6 ± 30.8       | 87.3 ± 32.8       | 0.222    |
| 1 o'clock               | 83.1 ± 27.3                 | 83.0 ± 26.4      | 83.5 ± 27.6       | 82.8 ± 27.9       | 0.937    |
| Nasal                   |                             |                   |                   |                   |          |
| 2 o'clock               | 65.4 ± 22.0                 | 65.7 ± 22.1      | 65.3 ± 22.9       | 65.3 ± 21.2       | 0.972    |
| 3 o'clock               | 53.0 ± 17.5                 | 53.3 ± 16.1      | 52.8 ± 14.6       | 52.7 ± 21.1       | 0.703    |
| 4 o'clock               | 55.6 ± 17.5                 | 56.6 ± 17.7      | 56.7 ± 17.2       | 53.6 ± 17.7       | 0.181    |
| Inferior                |                             |                   |                   |                   |          |
| 5 o'clock               | 76.4 ± 24.6                 | 77.4 ± 25.5      | 77.6 ± 25.5       | 74.2 ± 22.6       | 0.625    |
| 6 o'clock               | 83.3 ± 35.8                 | 82.1 ± 33.3      | 86.9 ± 36.7       | 80.9 ± 37.1       | 0.206    |
| 7 o'clock               | 73.1 ± 39.7                 | 72.1 ± 38.0      | 74.6 ± 38.5       | 72.6 ± 42.5       | 0.605    |
Table 5 (continued)

| Variable                  | Total (reference) (n = 458) | Low BAP (n = 153) | Mid BAP (n = 152) | High BAP (n = 153) | P value |
|---------------------------|-------------------------------|-------------------|-------------------|-------------------|---------|
| Disc topography           |                               |                   |                   |                   |         |
| Disc area                 | 2.06±0.75                     | 2.06±0.69         | 2.05±0.77         | 2.06±0.80         | 0.895   |
| Cup area                  | 1.52±0.78                     | 1.53±0.71         | 1.52±0.78         | 1.52±0.86         | 0.643   |
| Rim area                  | 0.54±0.42                     | 0.53±0.48         | 0.53±0.40         | 0.54±0.38         | 0.622   |
| Cup volume                | 0.43±0.36                     | 0.45±0.35         | 0.43±0.32         | 0.43±0.41         | 0.747   |
| Rim volume                | 0.05±0.07                     | 0.05±0.08         | 0.05±0.07         | 0.05±0.06         | 0.592   |
| C/D area ratio            | 0.72±0.20                     | 0.73±0.20         | 0.71±0.22         | 0.71±0.19         | 0.555   |
| Linear C/D ratio          | 0.84±0.14                     | 0.84±0.13         | 0.83±0.16         | 0.84±0.12         | 0.513   |
| Vertical C/D ratio        | 0.86±0.15                     | 0.88±0.13         | 0.85±0.17         | 0.86±0.13         | 0.290   |
| Disc diameter (V)         | 1.66±0.25                     | 1.67±0.24         | 1.66±0.25         | 1.65±0.27         | 0.422   |
| Disc diameter (H)         | 1.57±0.31                     | 1.57±0.31         | 1.56±0.31         | 1.57±0.31         | 0.957   |
| Macular GCC thickness (µm)|                               |                   |                   |                   |         |
| Total                     | 78.0±14.7                     | 78.8±14.4         | 80.5±15.2         | 80.7±14.6         | 0.557   |
| Superior                  | 83.5±17.0                     | 81.4±16.2         | 84.5±18.1         | 84.6±16.6         | 0.195   |
| Inferior                  | 76.5±15.6                     | 76.3±15.8         | 76.4±15.4         | 76.7±15.8         | 0.856   |

Asterisks: ** indicates \( p < 0.05 \), *** indicates \( p < 0.01 \). Mid Middle, cIOP Corrected pre-treatment intraocular pressure, CCT Central corneal thickness, BAP Biological antioxidant potential, AL Axial length, dBP Dilated blood pressure, cMT Corrected mean blur rate in the tissue area of the optic nerve, postIOP Post-treatment IOP with applanation tonography, MD Mean deviation, measured with the Humphrey visual field analyzer, PSD Pattern standard deviation, C/D Cup-disc ratio.
Table 6  Characteristics of glaucoma patients divided into three groups based on low, medium, or high cMT

| Variable                        | Total (reference) (n = 458) | Low MT (n = 153) | Mid MT (n = 152) | High MT (n = 153) | Pvalue |
|---------------------------------|-----------------------------|------------------|------------------|-------------------|--------|
|                                 |                             | Low—Mid         | Low—High         | Mid—High          |        |
| cMT (arbitrary units)           | 9.9 ± 2.6                   | 7.4 ± 1.6        | 9.8 ± 1.3        | 12.6 ± 1.8        | 0.004 **|
| Male / female                   | 244 / 214                   | 95 / 58          | 83 / 69          | 66 / 87           | 0.004 **|
| cOP (mmHg)                      | 18.8 ± 7.0                  | 18.5 ± 6.6       | 18.9 ± 7.4       | 19.1 ± 7.0        | 0.730  |
| CCT (μm)                        | 516.6 ± 35.7                | 517.1 ± 35.1     | 512.4 ± 38.5     | 520.2 ± 33.1      | 0.160  |
| BAP (μmol/L)                    | 2127.3 ± 284.9              | 2140.1 ± 251.4   | 2127.0 ± 299.1   | 2149.0 ± 303.6    | 0.966  |
| AL (mm)                         | 25.4 ± 2.1                  | 25.7 ± 1.7       | 25.5 ± 1.9       | 25.2 ± 1.9        | 0.087  |
| dBP (mmHg)                      | 76.8 ± 13.6                 | 75.8 ± 13.7      | 77.6 ± 14.2      | 76.9 ± 13.1       | 0.755  |
| cIOP (mmHg)                     | 18.8 ± 7.0                  | 18.5 ± 6.6       | 18.9 ± 7.4       | 19.1 ± 7.0        | 0.730  |
| postOP (mmHg)                   | 14.8 ± 4.7                  | 14.5 ± 4.7       | 14.4 ± 4.5       | 15.6 ± 4.7        | 0.007 **|
| Age (years)                     | 56.7 ± 14.4                 | 55.1 ± 15.9      | 57.1 ± 13.9      | 57.9 ± 13.2       | 0.370  |
| MD (dB)                         | -8.9 ± 7.8                  | -9.6 ± 8.7       | -9.1 ± 7.4       | -8.1 ± 7.1        | 0.443  |
| PSD (dB)                        | 8.0 ± 4.4                   | 7.6 ± 4.2        | 8.5 ± 4.4        | 9.0 ± 4.6         | 0.205  |
| Total cpRNFLT (μm)              | 71.4 ± 17.5                 | 69.4 ± 19.5      | 70.1 ± 16.0      | 74.8 ± 16.4       | 0.004 **|
| Quadrant cpRNFLT (μm)           |                             |                  |                  |                   |        |
| 4_Temporal                      | 64.5 ± 20.5                 | 62.6 ± 21.5      | 61.8 ± 19.5      | 69.3 ± 19.9       | <0.001 ***|
| 4_Superior                      | 85.6 ± 27.3                 | 82.2 ± 29.1      | 84.2 ± 25.7      | 90.4 ± 26.4       | 0.013 * |
| 4_Nasal                         | 58.0 ± 16.5                 | 57.2 ± 19.0      | 59.1 ± 15.3      | 57.8 ± 15.2       | 0.692  |
| 4_Inferior                      | 77.6 ± 28.5                 | 75.7 ± 30.1      | 75.1 ± 26.3      | 81.9 ± 28.6       | 0.043 * |
| 12-sector clockwise cpRNFLT (μm)|                             |                  |                  |                   |        |
| Temporal 8 o'clock              | 60.9 ± 24.7                 | 60.1 ± 28.9      | 57.8 ± 21.6      | 64.7 ± 22.5       | 0.002 **|
| 9 o'clock                       | 61.1 ± 19.2                 | 59.3 ± 20.3      | 59.0 ± 17.7      | 65.0 ± 18.9       | <0.001 ***|
| 10 o'clock                      | 71.5 ± 28.6                 | 68.5 ± 29.8      | 68.6 ± 26.9      | 77.4 ± 28.3       | 0.002 **|
| Superior 11 o'clock             | 87.9 ± 39.9                 | 84.4 ± 39.5      | 84.5 ± 38.3      | 94.7 ± 39.6       | 0.022 * |
| 12 o'clock                      | 85.8 ± 31.5                 | 82.1 ± 32.7      | 84.6 ± 29.8      | 90.7 ± 31.5       | 0.045 * |
| 1 o'clock                       | 83.1 ± 27.3                 | 80.3 ± 29.8      | 83.6 ± 25.6      | 85.6 ± 26.1       | 0.171  |
| Nasal                           | 65.4 ± 22.0                 | 64.3 ± 24.1      | 67.0 ± 20.5      | 65.0 ± 21.3       | 0.466  |
| 2 o'clock                       | 53.0 ± 17.5                 | 52.4 ± 15.4      | 54.2 ± 15.4      | 53.2 ± 14.4       | 0.717  |
| 3 o'clock                       | 55.6 ± 17.5                 | 54.7 ± 18.7      | 56.2 ± 18.0      | 56.0 ± 15.8       | 0.715  |
| Inferior 5 o'clock              | 76.4 ± 24.6                 | 72.4 ± 25.1      | 76.4 ± 24.6      | 80.4 ± 23.5       | 0.005 **|
| 6 o'clock                       | 83.3 ± 35.8                 | 80.5 ± 36.8      | 81.5 ± 33.7      | 87.8 ± 36.4       | 0.115  |
| 7 o'clock                       | 73.1 ± 39.7                 | 74.1 ± 41.8      | 67.5 ± 35.1      | 77.5 ± 41.2       | 0.091  |
Table 6 (continued)

| Variable                  | Total (reference) (n = 458) | Low MT (n = 153) | Mid MT (n = 152) | High MT (n = 153) | P value   | Low—Mid | Low—High | Mid—High |
|---------------------------|-----------------------------|------------------|------------------|------------------|-----------|---------|----------|----------|
| Disc topography           |                             |                  |                  |                  |           |         |          |          |
| Disc area                 | 2.06 ± 0.75                 | 2.29 ± 0.89      | 2.04 ± 0.60      | 1.84 ± 0.60      | < 0.001 *** | 0.015 * | < 0.001 *** | < 0.001 *** |
| Cup area                  | 1.52 ± 0.78                 | 1.78 ± 0.96      | 1.52 ± 0.62      | 1.26 ± 0.64      | < 0.001 *** | 0.097   | < 0.001 *** | < 0.001 *** |
| Rim area                  | 0.54 ± 0.42                 | 0.51 ± 0.46      | 0.52 ± 0.39      | 0.57 ± 0.42      | 0.128      |         |          |          |
| Cup volume                | 0.43 ± 0.36                 | 0.53 ± 0.47      | 0.43 ± 0.29      | 0.34 ± 0.26      | < 0.001 *** | 0.186   | < 0.001 *** | 0.012 *  |
| Rim volume                | 0.05 ± 0.07                 | 0.05 ± 0.09      | 0.05 ± 0.06      | 0.06 ± 0.06      | 0.007 **   | 0.676   | 0.008 **  | 0.057    |
| C/D area ratio            | 0.72 ± 0.20                 | 0.75 ± 0.21      | 0.74 ± 0.18      | 0.67 ± 0.21      | < 0.001 *** | 0.450   | < 0.001 *** | 0.010 **  |
| Linear C/D ratio          | 0.84 ± 0.14                 | 0.85 ± 0.14      | 0.85 ± 0.13      | 0.81 ± 0.15      | < 0.001 *** | 0.463   | < 0.001 *** | 0.010 *  |
| Vertical C/D ratio        | 0.86 ± 0.15                 | 0.88 ± 0.14      | 0.88 ± 0.14      | 0.83 ± 0.15      | < 0.001 *** | 0.912   | < 0.001 *** | < 0.001 *** |
| Disc diameter (V)         | 1.66 ± 0.25                 | 1.75 ± 0.30      | 1.65 ± 0.21      | 1.57 ± 0.22      | < 0.001 *** | 0.006 ** | < 0.001 *** | < 0.001 *** |
| Disc diameter (H)         | 1.57 ± 0.31                 | 1.65 ± 0.34      | 1.56 ± 0.27      | 1.48 ± 0.29      | < 0.001 *** | 0.023 * | < 0.001 *** | 0.004 **  |
| Macular GCC thickness (μm)|                             |                  |                  |                  |           |         |          |          |
| Total                     | 78.0 ± 14.7                 | 77.2 ± 16.0      | 78.3 ± 13.5      | 84.4 ± 13.6      | < 0.001 *** | 0.452   | < 0.001 *** | < 0.001 *** |
| Superior                  | 83.5 ± 17.0                 | 79.5 ± 17.3      | 82.2 ± 16.4      | 88.7 ± 16.1      | < 0.001 *** | 0.252   | < 0.001 *** | < 0.001 *** |
| Inferior                  | 76.5 ± 15.6                 | 75.0 ± 16.6      | 74.3 ± 14.2      | 80.0 ± 15.5      | 0.002 **   | 1.000   | 0.009 **  | 0.006 **  |

Asterisks: ** indicates p < 0.05, ***p < 0.01, and ****p < 0.001. Mid Middle, cIOP Corrected pre-treatment intraocular pressure, CCT Central corneal thickness, BAP Biological antioxidant potential, AL Axial length, dBP Dilated blood pressure, cMT Corrected mean blur rate in the tissue area of the optic nerve, postIOP Post-treatment IOP with applanation tonography, MD Mean deviation, measured with the Humphrey visual field analyzer, PSD Pattern standard deviation, C/D Cup-disc ratio
and superior cpRNFLT loss, but not inferior cpRNFLT loss [18, 52]. Thus, decreased OBF in the ONH can be either the cause or the result of glaucoma.

This study had several limitations. First, it was cross-sectional and included subjects from only a single hospital and a single ethnicity (Japanese). Second, when we investigated structural differences and their relationships with various risk factors in glaucoma patients, we found that it might have been better to exclude patients with myopia due to the variety of appearances a myopic disc can have. However, in Asia, mild to moderate myopia is a major risk factor for glaucoma [2], making it difficult to completely exclude myopia from this study. Therefore, we only excluded cases with severe myopia, to minimize the effect of myopia. Third, in Japan, older generations tend to have emmetropia and younger generations tend to have myopia. This generational bias might also have influenced our results. In order to minimize treatment bias, we recruited as many subjects as possible (over 450 eyes). In the near future, we would like to perform a study that classifies cases with constant parameters, such as genetics, that would result in a more stable classification of glaucoma. Fourth, this study was part of ongoing exploratory research with the goal of classifying glaucoma based on specific risk factors and developing new glaucoma treatment algorithms. In this study, as a first step, we investigated the relationship between measurable risk factors and damage type in glaucoma, including in the macula and optic nerve head. Our findings revealed many differences and associations, but did not allow us to form a clear hypothesis on expected risk profiles. Further study is needed to obtain succinct, conclusive findings that will benefit health care providers and patients.

**Conclusion**

In conclusion, this study identified subgroups of glaucoma patients with differing risk factors. These patients tended to have unique phenotypes, and we found that they have risk factors that were IOP-independent. Our findings suggest that there is at least one category of glaucoma patients for whom different risk factors contribute to the pathophysiology of glaucoma, and that these patients may benefit from treatments that target these risk factors. We consider that mechanism-dependent treatment is a reasonable approach to glaucoma care, and that our approach to the clinical measurement of risk factors may open new avenues for the individual treatment of glaucoma.

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**Authors’ contributions**

TN contributed to design of the work, management of the work, and writing the manuscript. KO contributed to data analysis and writing the manuscript. TK, MA, and NT contributed to data collection and provided technical support. ST, NH, TN, NT, SK contributed to data collection, data analysis and interpretation of data. KP contributed to data analysis. The authors read and approved the final manuscript.

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**Availability of data and materials**

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

**Declarations**

**Ethics approval and consent to participate**

This study adhered to the tenets of the Declaration of Helsinki, and the protocols were approved by the Clinical Research Ethics Committee of the Tohoku University Graduate School of Medicine (study 2021-1-430). Our ethics committee allowed us to waive written informed consent from the patients, because we used retrospective data from patients who received insured medical treatment and opted out of consent requests. No patient was individually identified in this study.

**Consent for publication**

Not applicable.

**Competing interests**

Coauthors TK, NT, and MA are employed by Topcon Corporation, a commercial company. There are no patents, products in development or marketed products to declare. The other authors have no potential conflicts of interest associated with this manuscript.

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