• Clinical Research •

Relationship between corneal stiffness and glaucoma severity: clinical insights from Corvis ST technology

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Abstract

● **AIM:** To explore the mechanical indices used for differential diagnosis and to investigate the relationship between ocular biomechanics and glaucoma severity within each group.

● **METHODS:** This cross-sectional study included 185 eyes from 185 subjects: 62 normal controls, 91 high-tension glaucoma (HTG), and 32 normal-tension glaucoma (NTG) patients. All participants underwent a comprehensive ophthalmic examination that involved ocular biomechanical measurements. Glaucoma severity was assessed using visual field index (VFI), mean deviation (MD), pattern standard deviation (PSD) and retinal nerve fiber layer (RNFL) thickness. Multivariable models were used to compare fifteen biomechanical parameters among the three groups adjusting for age, gender, intraocular pressure (IOP), central corneal thickness (CCT), and axial length (AL). The generalized linear model was utilized for multifactor comparison.

● **RESULTS:** Significant differences in first applanation time (AT1), highest concavity time (HC time), stress strain index (SSI), and HC deflection were found among the three groups (P<0.05). AT1 was significantly higher in the HTG group compared to controls (P<0.05), and SSI was higher in HTG than NTG (P<0.05). HC deflection in the HTG group was significantly smaller than in NTG (P<0.05). Furthermore, AT1 levels were observed to be significantly higher in primary open angle glaucoma (POAG) patients compared to controls (P<0.05). Receiver operating charactristic (ROC) analysis showed HC deflection had an area under the curve (AUC) of 0.802 between HTG and NTG. A negatively significant correlation was observed between SSI and VFI in POAG patients.

● **CONCLUSION:** Biomechanical analysis reveals that corneas in POAG patients are stiffer than normal controls, with increased corneal stiffness correlating with more severe glaucomatous damage. Interestingly, stiffer corneas in NTG patients appeares protective. In addition, HC deflection may be useful for differentiating HTG and NTG.

● **KEYWORDS:** corneal biomechanics; glaucoma; primary open angle glaucoma; normal-tension glaucoma

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INTRODUCTION

Glaucoma, recognized as the second leading cause of blindness worldwide, is characterized by optic nerve atrophy and visual field defects. Intraocular pressure (IOP) serves as the primary influencing factor[1]. Primary open angle glaucoma (POAG), the most prevalent type, encompasses high-tension glaucoma (HTG) with elevated IOP and normal-tension glaucoma (NTG), where IOP remains within the normal range. The clinical manifestations of POAG are typically characterized by an increased cup-to-disc ratio, loss of optic nerve fiber bundles, specific visual field defects, and asymmetric progression[2]. Pathologically, it entails retinal ganglion cell (RGC) damage and progressive degeneration of the optic nerve[3-4]. Controlling IOP is the primary factor in managing glaucoma treatment[3,5-6]. Despite effective IOP-

lowering strategies, many patients continue to experience disease progression, suggesting the involvement of additional risk factors beyond IOP[7].

Recent studies have shifted attention to the biomechanical properties of ocular tissues, particularly the cornea, as potential contributors to glaucoma pathophysiology[8-12]. Changes in the extracellular matrix (ECM) are believed to play a pivotal role in the augmented outflow resistance of the trabecular reticulum (TM)[13-14], and the ECM might serve as a contributing factor in impaired aqueous drainage and elevated IOP in POAG[15-16]. The ECM composition of the cornea, TM, sclera, and lamina cribrosa (LC) shares a similarity in their predominant fibrous collagen content. In glaucoma, the increased deformability of the cornea, which is part of a structural continuum with the sclera and LC, may reflect enhanced deformability of these tissues, making the optic nerve head more vulnerable to damage[17-19]. Consequently, the biomechanical properties of LC could potentially be influenced by those of the cornea. The researchers hypothesized that the stiffening of ocular structures, including the cornea, sclera, and LC, could play a role in the development of glaucoma[20]. Thus, alterations in corneal physiology among glaucoma patients can indirectly reflect changes in optic nerve head compliance, relating to compression and injury to the LC[21-22], a key site of glaucomatous damage, while the direct measurement of LC mechanical parameters remains challenging, making the assessing of corneal characteristics a valuable method for indirectly predicting scleral and LC mechanical properties. Therefore, researchers have initiated investigations to explore the association between corneal biomechanics and glaucoma severity[18,23]. These hypotheses underscore the importance of corneal biomechanics as a surrogate marker for understanding glaucomatous damage[12].

Some researchers have found that individuals with glaucoma exhibit greater ocular rigidity compared to healthy controls, as evidenced by both *in vivo* and *in vitro* studies[13,22,24-26]. However, other researchers propose that eyes with glaucoma tend to display lower ocular rigidity compared to healthy eyes matched for aged, IOP, and axial length (AL)[27]. Interestingly, Leung *et al*[28] did not observe statistically significant differences in corneal biomechanics between POAG patients and the control group in their study. We have also noted that there is a prevailing consensus within the academic community that glaucoma patients with low corneal hysteresis and low central corneal thickness (CCT) exhibit more severe visual field and retinal nerve fiber layer (RNFL) damage[15,18,29-31], as supported by various studies. Qassim *et al*[18] suggested that eyes with high corneal stiffness parameters experience more rapid thinning of RNFL and are more likely to suffer progressive visual field loss. However, other researchers contend that stiffer eyes exhibit less damage to RGCs[32-33]. The limited number of studies on corneal biomechanics and glaucoma severity using the Corneal Visualization Scheimpflug Technology (Corvis ST) and the conflicting conclusions underscore the need for further investigation[18,22-23,32,34-37]. Therefore, this study aims to address these gaps by utilizing Corvis ST to analyze corneal biomechanical parameters in HTG, NTG, and control groups. By integrating demographic data, detailed medical histories, and glaucoma severity indices such as visual field index (VFI) and RNFL thickness, we seek to clarify the relationship between corneal biomechanics and glaucoma severity. Additionally, we investigate whether biomechanical differences can aid in distinguishing HTG from NTG, providing insights into their distinct pathophysiological mechanisms and informing targeted management strategies.

PARTICIPANTS AND METHODS

Ethical Approval This was a cross-sectional study conducted at West China Hospital, Sichuan University, with data being collected from June 2022 to April 2023. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of West China Hospital (Chengdu), China. Informed consent was obtained from the subjects prior to the enrollment.

Participants The study involved 185 eyes from 185 subjects, including 62 normal controls (control group), 91 patients with HTG (HTG group), and 32 patients with NTG (NTG group). Normal controls, characterized by an IOP less than 21 mm Hg, normal retinal and optic disc appearance, and absence of other ocular or systemic diseases, were recruited from refractive surgery centers. Patients were diagnosed with POAG by a trained and experienced glaucoma specialist based on the appearance of the optic nerve head in glaucoma, glaucomatous visual field defects, and the open angles on gonioscopy. Glaucoma patients were classified as HTG based on an IOP greater than 21 mm Hg, or NTG when IOP less than 21 mm Hg since examination (the 24-hour IOP of each patient was also less than 21 mm Hg).

Exclusion criteria included participants under 18 or over 75 years old, pregnant individuals, and those unable to complete ophthalmic exams. Individuals with ocular or periocular trauma, best-corrected visual acuity worse than 0.5, spherical equivalent <-6.00 diopters (D), refractive surgery, or a history of uveitis, retinal disease, corneal opacities, dystrophy, degeneration, or keratoconus were excluded. Also excluded were those using prostaglandin analogs or corticosteroids (past or present), those with ocular disease affecting corneal biomechanics, and individuals who wore contact lenses within three weeks. Finally, participants with ocular or systemic diseases affecting the optic nerve or visual field were not eligible.

Ophthalmic Examinations All participants underwent a comprehensive ophthalmic examination, including the evaluation best-corrected visual acuity, measurement IOP (mean of 3 measurements) using non-contact tonometer, slit-lamp biomicroscopy, gonioscopy (Volk 4-mirror, Volk Optical, Inc., USA), optic disc photography (NW500,Topcon Corporation, Tokyo, Japan), CCT measurement *via* ultrasound pachymetry (Tomey Corporation, Nagoya, Japan), AL measurement using IOL Master (Carl Zeiss Meditec, Jena, Germany), and automated perimetry with the 24-2 Swedish Interactive Threshold Algorithm (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA, USA) were performed. The VFI, mean deviation (MD), and pattern standard deviation (PSD) were recorded. Visual field reliability was established with fixation losses less than 20%, and false-positive rates and false-negative rates less than 15%; only reliable visual fields were included in the assessments[23]. Corneal tomography was conducted using the Pentacam (Oculus, Wetzlar, Germany), and the RNFL was measured using optical coherence tomography (CIRRUS HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Corneal biomechanics were measured using the Corvis ST (Corvis ST, Oculus, Germany). Detailed medical histories of each subject were also recorded.

Corvis ST Tonometer Measurements Measurements using the Corneal Visualization Scheimpflug Technology instrument (Corvis ST, software ver. 1.6b2507; Oculus) were conducted three times for each eye. The dynamic ultra-high-speed Scheimpflug camera captures 140 digital frames at a resolution of 640×480 pixels within 30ms, detailing the deformation response of the central 8.5 mm of the cornea[22]. The principles and procedures for measuring dynamic corneal response parameters using Corvis ST, along with the interpretation of these parameters, have been extensively discussed in the existing literature[23,32,34,37-40]. After each measurement, patients were given a rest period of at least 90s. All Corvis ST measurements were automatically captured when aligned with the corneal apex, ensuring sufficient reliability, and were considered valid when the “OK” quality index appeared on the Corvis ST monitor.

The clinical significance of corneal biomechanical parameters has been comprehensively summarized in recent papers[40]. It has been established that lower values of first applanation velocity (A1 velocity, AV1), deformation amplitude (DA), peak distance (PD), and integrated radius indicate increased corneal stiffness[41]. Conversely, higher values for these parameters suggest a greater propensity for corneal deformation[23,32,37]. In contrast, lower values of first applanation time (AT1), highest concavity time (HC time), highest concavity deflection (HC deflection), stiffness parameter A1 (SP-A1), Ambiosio relational thickness horizontal (ARTH) and stress strain index (SSI) are indicative of a higher likelihood for corneal deformation[23,32,37], whereas higher values of these metrics are associated with increased corneal stiffness[42]. It is noteworthy that a smaller value of whole eye movement (WEM) indicates smaller orbital compliance[23].

Statistical Analysis For statistical analysis, data from only one eye per subject were included. To prevent selection bias, data from the right eye only were included in the statistical analysis when both eyes met the inclusion criteria. Data following a normal distribution are expressed as mean±standard deviation (SD), whereas data not following normal distribution are presented as medians and interquartile ranges.

The analysis of variance (ANOVA) or Kruskal-Wallis rank sum test was utilized to evaluate differences in demographic and eye parameters among the normal control, NTG, and HTG groups. A generalized linear model was applied to analyze biomechanical differences among the three groups. Additionally, the Bonferroni post hoc test was employed for pairwise comparisons. The receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic value of mechanical parameters.

The Pearson correlation coefficient was calculated to explore potential correlating factors with the glaucoma severity index. A generalized linear model was utilized to assess the relationship between glaucoma severity parameters and demographic and ocular variables across each group. In this study, the significance level (P-value) was set at <0.05 (two-tailed), and the entire analysis was conducted using the statistical analysis software SAS 9.4. The figures were generated using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics Table 1 presents the demographic and ocular characteristics of all participants. All indicators of glaucoma severity (VFI, MD, PSD, RNFL), along with gender, age, IOP, and AL (except for CCT), exhibited significant differences among the three groups (P<0.05).

Comparison of Mechanical Parameters Among Groups The corneal biomechanical differences among the three groups were analyzed using gender, age, IOP, AL and CCT as variables in the generalized linear model (Table 2). AT1, HC time, SSI and HC deflection demonstrated statistically significant differences among these three groups (P<0.05). There was a significantly increase in AT1 in the HTG group compared to the control group (P<0.05). The SSI in the HTG group was significantly higher than that in the NTG group (P<0.05), while the HC deflection was significantly smaller than that of the NTG group (P<0.05). However, no significant difference observed in HC time during the pairwise

Table 1 Demographic and characteristics among control group, HTG, and NTG group

Variables	Control (*n*=62)	HTG (*n*=91)	NTG (*n*=32)	*P*	*P1*	*P2*	*P3*
Gender (male/female)	17/45	65/26	23/9	<0.001[a]	<0.001[a]	<0.001[a]	0.962
Age, y	30 (24, 33)	58 (52, 67)	66 (50, 71)	<0.001[a]	<0.001[a]	<0.001[a]	0.135
IOP, mm Hg	16 (15, 18)	18 (16, 21)	15 (14, 18)	<0.001[a]	<0.001[a]	0.211	<0.001[a]
AL, mm	24.88 (23.84, 25.88)	23.98 (23.16, 24.76)	24.10 (22.93, 25.91)	0.001[a]	<0.001[a]	0.210	0.836
CCT, μm	534.29±37.436	536.62±35.514	526.53±30.053	0.382	0.314	0.690	0.166
MD, dB	-1.64 (-2.24, -0.66)	-8.69 (-18.70, -2.82)	-9.98 (-17.56, -3.37)	<0.001[a]	<0.001[a]	<0.001[a]	0.980
PSD, dB	1.65 (1.38, 1.99)	5.90 (2.36, 10.88)	7.77 (2.46, 10.52)	<0.001[a]	<0.001[a]	<0.001[a]	0.927
VFI	97 (88, 101)	68 (56, 79)	69 (62, 84)	<0.001[a]	<0.001[a]	<0.001[a]	0.513
RNFL, μm	98 (97, 99)	75 (45, 97)	71 (50, 95)	<0.001[a]	<0.001[a]	<0.001[a]	0.934

P: *P* value of three groups; *P1*: *P* value between control group and HTG group; *P2*: *P* value between control group and NTG group; *P3*: *P* value between HTG group and NTG group. HTG: High-tension glaucoma; NTG: Normal-tension glaucoma; IOP: Intraocular pressure; AL: Axial length; CCT: Central corneal thickness; MD: Mean deviation; PSD: Pattern standard deviation; VFI: Visual field index; RNFL: Retinal nerve fiber layer. [a]*P*<0.05.

Table 2 Adjusted ocular biemechanical parameters and comparative analysis among groups of control, HTG, and NTG

Variables	Control (*n*=62)	HTG (*n*=91)	NTG (*n*=32)	*P*	*P1*	*P2*	*P3*
AT1	7.72±0.03	7.83±0.02	7.81±0.03	0.015[a]	0.011[a]	0.102	1.000
AV1	0.13±0.00	0.13±0.00	0.13±0.00	0.170	1.000	1.000	0.206
AT2	21.14±0.29	21.51±0.19	21.68±0.29	0.533	1.000	0.789	1.000
AV2	-0.24±0.01	-0.24±0.00	-0.25±0.01	0.290	1.000	0.858	0.369
HC time	16.77±0.11	17.01±0.07	16.74±0.11	0.033[a]	0.342	1.000	0.062
PD	4.58±0.03	4.56±0.02	4.64±0.04	0.159	1.000	0.860	0.167
HC Radius	7.42±0.28	7.01±0.19	7.51±0.29	0.208	0.943	1.000	0.327
SPA1	114.57±2.56	116.50±1.72	113.34±2.64	0.500	1.000	1.000	0.784
ARTH	494.15±21.01	508.46±14.12	488.4±21.62	0.648	1.000	1.000	1.000
SSI	1.26±0.04	1.25±0.03	1.15±0.04	0.039[a]	1.000	0.220	0.040[a]
WEM length	0.25±0.02	0.24±0.01	0.26±0.02	0.486	1.000	1.000	0.719
WEM time	22.01±0.25	21.75±0.17	21.89±0.25	0.692	1.000	1.000	1.000
HC deflection	0.79±0.01	0.79±0.01	0.83±0.01	0.007[a]	1.000	0.125	0.006[a]
Integrated Radius	8.08±0.16	8.10±0.11	8.30±0.17	0.502	1.000	1.000	0.768
DA ratio 2 mm	4.27±0.06	4.31±0.04	4.42±0.06	0.217	1.000	0.419	0.353

P: General linear model with adjustment for gender, age, AL, IOP, and CCT; *P1*: Bonferroni post hoc tests between control group and HTG group; *P2*: Bonferroni post hoc tests between control group and NTG group; *P3*: Bonferroni post hoc tests between HTG group and NTG group. [a]*P*<0.05. HTG: High-tension glaucoma; NTG: Normal-tension glaucoma; AT1: First applanation time; AV1: First applanation velocity; AT2: Second applanation time; AV2: Second applanation velocity; HC: Highest concavity; PD: Peak distance; SPA1: Stiffness parameter-first applanation; ARTH: Ambiosio relational thickness horizontal; SSI: Stress strain index; WEM: Whole eye movement; DA: Deformation amplitude.

comparisons. Combining HTG and NTG into a single POAG group and analyzing it alongside the control group using the same method revealed that AT1 levels were significantly higher in the POAG group compared to the control group (P<0.05; Table 3).

Relationship Between Ocular Biomechanics and Glaucoma Severity Based on the results of Table 1, further ROC analysis was performed, revealing that the area under the curve (AUC) value for HC deflection was 0.802 when comparing the HTG group to the NTG group. However, the AUC values for SSI (HTG *vs* NTG) and AT1 (HTG *vs* Control) were both less than 0.7 (Table 4). Subsequent univariate analysis examining factors related to glaucoma severity indicated significant associations between various variables and MD, VFI, and RNFL (Figures 1 and 2). As depicted in Figure 1, age and SSI showed negative correlations with MD, VFI and RNFL in POAG group (P<0.05). Biomechanical parameters showing statistically significant differences in univariate analysis, gender, age, AL, CCT and IOP were included in multiple linear regression model. Thereout, SSI in the POAG group displayed a negative correlation with VFI (Figure 3). HTG and NTG were analyzed separately following the same methodology (Figures 2 and 4). In the HTG group, age and SSI exhibited a negative correlation with MD, VFI, and RNFL (P<0.05), while WEM length

Table 3 Adjusted ocular biemechanical parameters and comparativ analysis between groups of control group, and POAG

Variables	POAG	Control (*n*=62)	*P*
AT1	7.82±0.02	7.72±0.03	0.004[a]
AV1	0.13±0.00	0.13±0.00	0.638
AT2	21.55±0.18	21.15±0.29	0.328
AV2	-0.24±0.00	-0.24±0.01	0.759
HC time	16.94±0.07	16.76±0.11	0.226
PD	4.58±0.02	4.58±0.03	0.940
HC Radius	7.13±0.17	7.44±0.28	0.450
SPA1	115.72±1.58	114.45±2.56	0.728
ARTH	503.51±12.91	493.40±20.98	0.735
SSI	1.23±0.02	1.26±0.04	0.565
WEM length	0.25±0.01	0.25±0.02	0.813
WEM time	21.78±0.15	22.02±0.25	0.504
HC deflection	0.80±0.01	0.79±0.01	0.641
Integrated Radius	8.15±0.10	8.08±0.16	0.771
DA ratio 2 mm	4.34±0.04	4.28±0.06	0.439

POAG=HTG+NTG. POAG: Primary open angle glaucoma; HTG: High-tension glaucoma; NTG: Normal-tension glaucoma; AT1: First applanation time; AV1: First applanation velocity; AV2: Second applanation velocity; AT2: Second Applanation Time; HC: Highest concavity; PD: Peak distance; SPA1: Stiffness parameter-first applanation; ARTH: Ambiosio relational thickness horizontal; SSI: Stress strain index; WEM: Whole eye movement; DA: Deformation amplitude. [a]*P*<0.05.

Table 4 Results of the ROC analyses

Variables	AUC	95%CI	Cut-off	Sensitivity	Specificity
AT1 (HTG *vs* Control)	0.693	0.614-0.773	7.475	0.797	0.532
HC deflection (HTG *vs* NTG)	0.802	0.721-0.884	0.825	0.75	0.758
SSI (HTG *vs* NTG)	0.654	0.537-0.771	1.145	0.813	0.469

ROC: Receiver operating characteristic; AUC: Area under the ROC curve; CI: Confidence interval; AT1: First applanation time; HC: Highest concavity; HTG: High-tension glaucoma; NTG: Normal-tension glaucoma; SSI: Stress strain index.

showed a negative correlation with MD and VFI (*P*<0.05). In the NTG group, IOP, AT1 and SP-A1 demonstrated a positive correlation with RNFL (*P*<0.05), whereas PD, DA ratio 2 mm displayed a negative correlation with RNFL (*P*<0.05). However, upon further multifactor analysis did not identify any parameter as significantly associated with glaucoma severity.

DISCUSSION

Currently, the exact impact of ocular biomechanics on POAG damage remains unclear, although the clinical application of Corvis-ST shows considerable promise[37]. Consequently, this study aimed to gather and analyze biomechanical parameters among HTG patients, NTG patients, and control subjects. Furthermore, an assessment was conducted to ascertain the association with glaucoma severity. Notably, previous studies by Wu *et al*[23] and Vinciguerra *et al*[35] have identified significant differences in age, gender, and IOP across various groups. Since our healthy controls predominantly comprised individuals assessed before refractive surgery procedures at specialized centers, their AL was longer than that in the POAG group, attributed to higher diopter values commonly found in this population. However, these variables were accounted for in the statistical analysis without unduly restricting baseline data.

Regarding CCT (Table 1), our findings are in agreement with those of Wu *et al*[23], showing no significant difference between the NTG and HTG group. However, Xu *et al*[43] and Vinciguerra *et al*[35] demonstrated that the cornea in the NTG group exhibited a thinner profile compared to the HTG group, potentially attributed to distinct underlying pathogenic mechanism. Results from the general linear model analysis revealed significant differences among the three groups for AT1, HC time, SSI and HC deflection (Table 2). When combined with the Bonferroni post hoc test, AT1 results indicated that corneas in the HTG group were stiffer and less prone to deformation compared to the control group. SSI findings showed that corneas in the HTG group were stiffer than those in the NTG group, while HC deflection indicated greater deformability in the HTG group compared to the NTG group (Table 2). Notably, SSI serves as a novel parameter for assessing corneal stiffness, eliminating interference from IOP

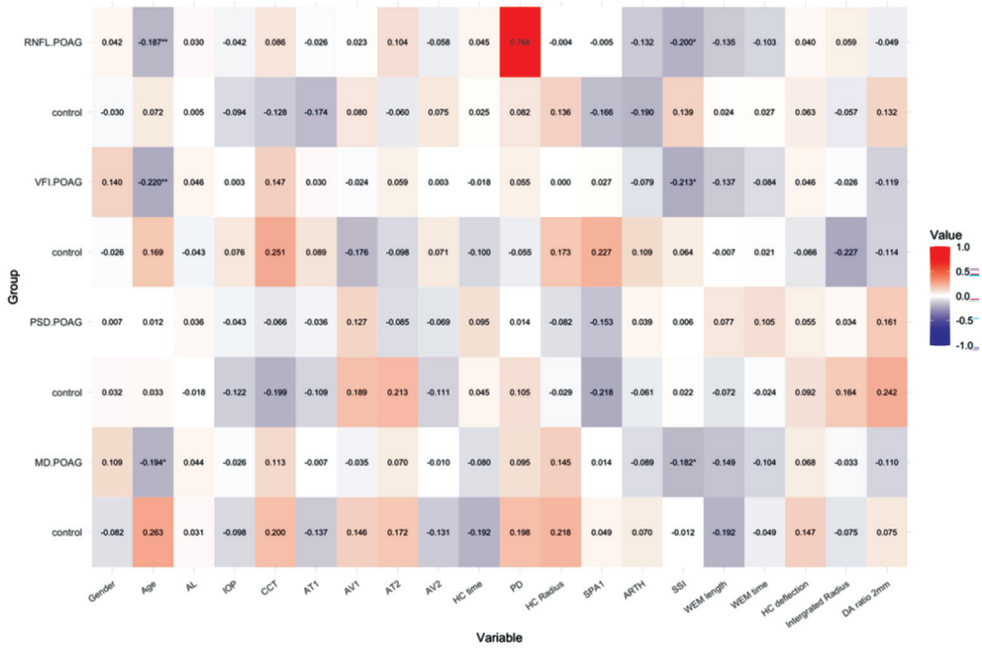

Figure 1 Correlation between demographic and ocular variables with glaucoma severity indices by univariate analysis in control and POAG groups POAG: Primary open angle glaucoma.

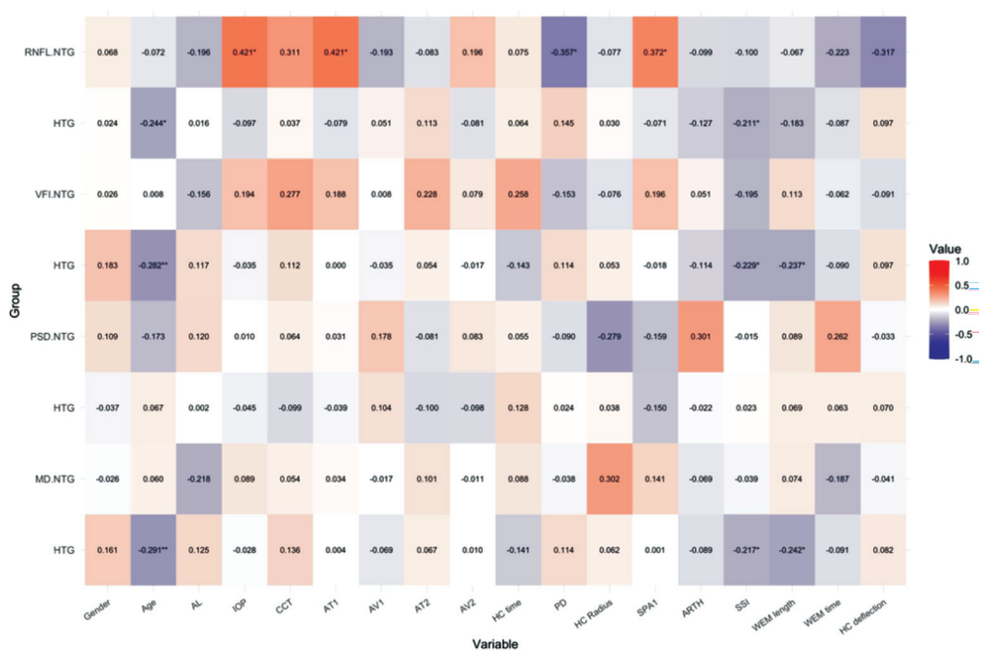

Figure 2 Correlation between demographic and ocular variables with glaucoma severity indices by univariate analysis in HTG control and NTG groups HTG: High-tension glaucoma; NTG: Normal-tension glaucoma.

and CCT and showing a positive correlation with age[44]. Our study found SSI results between the HTG group and the NTG group, suggesting a stiffer cornea in HTG without significant differences in age, which provides some level of data support. As for the observed inconsistencies in HC deflection results, the reasons remain unclear. Meanwhile, in the analysis comparing corneal stiffness between the total POAG and control groups, AT1 results also support the idea that POAG patients' corneas exhibit increased hardness and reduced deformation compared to healthy controls, aligning with previous studies[22,37,45]. However, some experts have reported that corneal deformability in POAG exceeds that in healthy controls[23,32]. Interestingly, there are also findings suggesting no significant difference in corneal hardness between these groups[28]. Further investigations using animal experiments or larger cohort studies are needed to conclusively determine these aspects.

Subsequently, we performed an analysis to investigate the potential of biomechanical parameters in the differential diagnosis of POAG. To evaluate their capability in differential

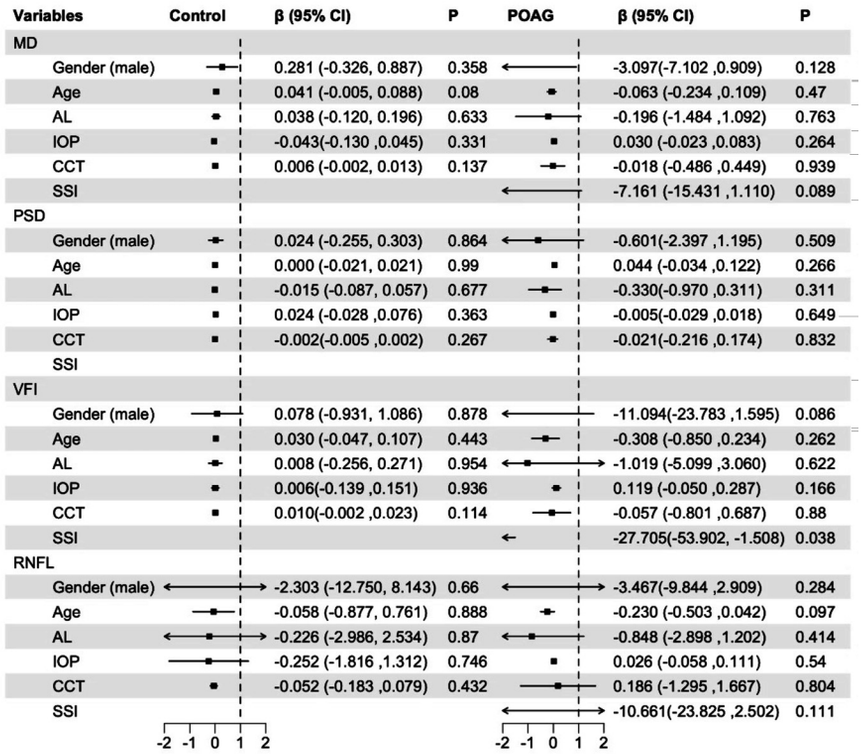

Figure 3 Association between demographic and ocular variables with glaucoma severity parameters by multivariate linear regression analysis in groups of normal control and POAG CI: Confidence interval; POAG: Primary open angle glaucoma; MD: Mean deviation; AL: Axial length; IOP: Intraocular pressure; CCT: Central corneal thickness; SSI: Stress strain index; PSD: Pattern standard deviation; VFI: Visual field Index; RNFL: Retinal nerve fiber layer.

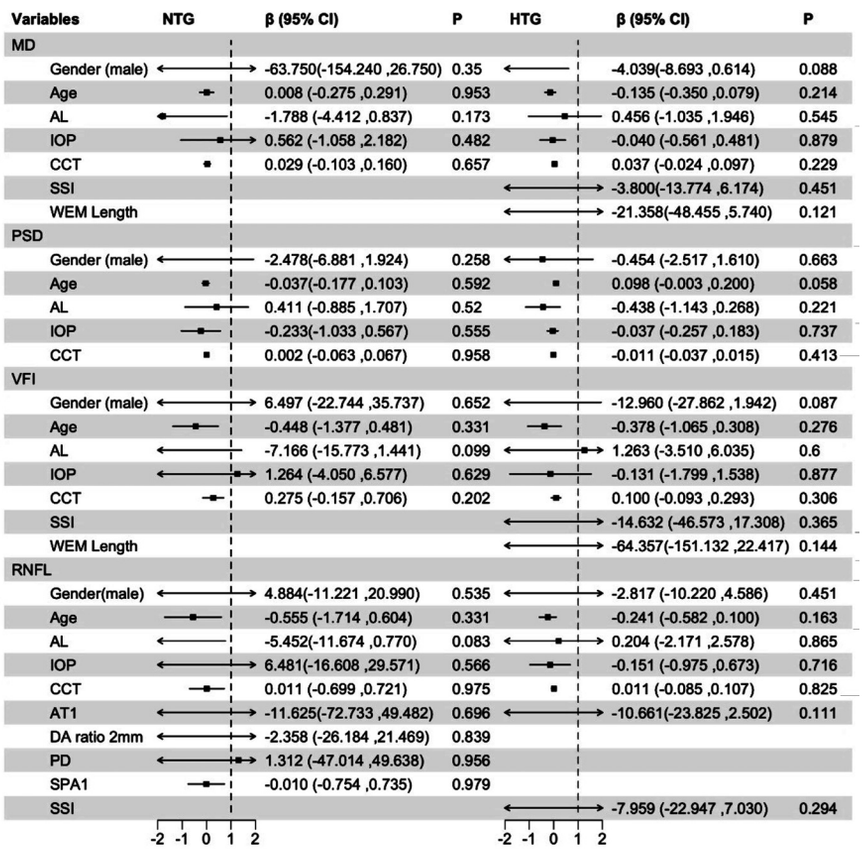

Figure 4 Association between demographic and ocular variables with glaucoma severity parameters by multivariate linear regression analysis in NTG and HTG groups NTG: Normal-tension glaucoma; CI: Confidence interval; HTG: High-tension glaucoma; AL: Axial length; IOP: Intraocular pressure; CCT: Central corneal thickness; SSI: Stress strain index; WEM: Whole eye movement; AT1: First applanation time; DA: Deformation amplitude; PD: Peak distance; SPA1: Stiffness parameter-first applanation.

diagnosis, we carried out ROC analysis on three parameters (Table 4). Our findings indicated that only HC deflection (HTG *vs* NTG) had an AUC exceeding 0.8, suggesting its potential utility in the differential diagnosis between HTG and the NTG group. In scenarios where continuous IOP monitoring is conducted over a 24-hour period for POAG, this significantly increases the medical burden. Under such circumstances, corneal biomechanical examination emerges as a promising diagnostic tool for NTG.

In a univariate analysis examing parameters associated with the severity of glaucoma, we identified negative correlations on age and SSI in the POAG group with MD, VFI and RNFL. POAG is recognized as an age-related neurodegenerative disease[46], and our findings concur that with increasing age, the disease severity tends to escalate. Furthermore, higher SSI values, indicative of a stiffer cornea, were associated with lower MD, VFI, and RNFL measurements, further suggesting increased disease severity. Expanding on these findings, our multivariate analysis demonstrated a negative correlation between VFI and SSI in the POAG group. Consequently, we hypothesize that SSI values could serve as potential predictors of glaucoma severity and early disease progression in future research. In separate analyses of HTG and NTG, we observed negative correlations between age and SSI with MD, VFI, and RNFL in the HTG group, aligning with previous findings and suggesting that advancing age is associated with increased ocular rigidity and potentially more severe optic nerve damage in glaucoma.

WEM length showed a negative correlation with MD and VFI exclusively in the HTG group. However, a shorter WEM time was demonstrated to be associated with worse glaucoma damage in NTG, but not in HTG[23]. This distinction underscores the importance of considering different glaucoma subtypes when analyzing corneal biomechanical properties and their relation to disease severity.

In the NTG group, a univariate analysis of four parameters (AT1, SPA1, PD, DA ratio 2 mm) revealed significant correlations between corneal stiffness and glaucoma-related RNFL injury. Specifically, a stiffer cornea with reduced susceptibility to deformation was associated with less optic nerve damage in glaucoma patients. This suggests that inherent corneal rigidity in NTG may provide a protective effect on the optic nerve. Additionally, in NTG, softer corneas were linked to greater LC curvature, making the optic nerve more susceptible to damage[47]. Previous studies have indicated that NTG patients exhibit greater corneal compliance and deformability compared to HTG individuals and healthy controls[14]. A recent prospective clinical cohort study by Xu *et al*[48] also demonstrated that NTG corneas are softer than those of HTG patients. This finding supports the notion that alterations in ocular biomechanics among NTG patients might contribute to their increased vulnerability to glaucoma[23,32,43] aligning with our research outcomes.

Interestingly, a positive correlation was observed between IOP and RNFL in NTG patients. It is well-documented that reducing IOP has a neuroprotective effect, potentially delaying or preventing structural and functional optic nerve damage in glaucoma patients, including those with NTG patients[49]. Compared to HTG, NTG is associated with higher ocular compliance[23,35], and within a certain range, higher IOP has a stronger supporting effect on the eyeball. Based on our statistical findings, we hypothesize that NTG patients might not require substantial reductions in IOP. A possible explanation is that in NTG patients, increased IOP may enhance ocular mechanical properties, providing some protective effect on the optic nerve. In multivariate analyses adjusting for factors like age, gender, IOP, CCT, and AL, no mechanical parameters were found to be associated with severity indicators in HTG and NTG.

Wu *et al*[23] observed that the AL in eyes with HTG correlated with glaucoma severity. Eyeball elongation is typically accompanied by a reduction in scleral collagen fiber bundles, leading to sclera and LC thinning, decreased scleral hardness, and increased ocular compliance. A longer AL is indicative of more extensive glaucoma-induced damage. An association between increased corneal deformability and AL elongation, and its potential role in the pathogenesis of NTG, has been suggested[22]. However, our studies have not found evidence supporting this correlation.

It is crucial to acknowledge the inherent limitations of the cross-sectional study design in our research. To thoroughly investigate the association between ocular biomechanics and glaucoma severity, along with disease progression, we recommend conducting further prospective studies with larger sample sizes across multiple centers. Cohort studies should be pursued when resources permit, offering an ideal approach to this research. Developing integrated measurement methods for both corneal and scleral biomechanics could provide more direct evidence[10]. Furthermore, it is essential to consider that population and racial differences among enrolled patients, as well as challenges in the reproducibility of Corvis ST measurements, might contribute to discrepancies between our findings and previous studies.

Our research provides a comprehensive analysis of ocular biomechanical parameters in the context of glaucoma, highlighting the potential of these parameters in differentiating between HTG and NTG. Notably, our findings elucidate the contrasting biomechanical properties associated with these glaucoma subtypes and suggest a unique protective role of corneal stiffness in NTG. Given the ongoing debate and the

paucity of conclusive data in this area, our study contributes valuable new evidence that furthers our understanding of glaucoma pathophysiology. In summary, the analysis of adjusted ocular biomechanical parameters indicated that the corneas in POAG patients are stiffer than those in normal controls, with stiffer corneas frequently associated with more severe glaucoma damage. However, in patients with NTG, stiffer corneas appear to offer some protective effects against glaucoma damage. Additionally, HC deflection may hold potential value in the differential diagnosis of HTG and NTG.

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