Natural History and Risk Factors for Glaucoma Progression in Chinese Patients With Normal-Tension Glaucoma

De-Fu Chen,[1,2] Chenmin Wang,[1,2] Yuqing Si,[1,2] Xiaonan Lu,[1,2] Weihe Zhou,[1] Qiangjie Huang,[1] Jingjing Zuo,[1,2] Gangwei Cheng,[3] Dexter Y. L. Leung,[4] Ningli Wang,[5] David S. Friedman,[6] and Yuanbo Liang[1,2]

[1]National Clinical Research Center for Ocular Diseases, Eye Hospital, Wenzhou Medical University, Wenzhou, China
[2]Glaucoma Research Institute, Wenzhou Medical University, Wenzhou, China
[3]Key Laboratory of Ocular Fundus Diseases, Department of Ophthalmology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
[4]Department of Ophthalmology, Hong Kong Sanatorium and Hospital, Hong Kong SAR, China
[5]Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology & Visual Science Key Lab, Beijing, China
[6]Glaucoma Center of Excellence, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, United States

Correspondence: Yuanbo Liang, National Clinical Research Center for Ocular Diseases, Eye Hospital, Wenzhou Medical University, No. 270, Xue Yuan Xi Road, Wenzhou 325000, China; yuanboliang@wmu.edu.cn.

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Purpose. To characterize the natural history of normal-tension glaucoma (NTG) in Chinese patients.

Methods. The prospective observational cohort study included patients with untreated NTG with a minimum follow-up of 2 years. Functional progression was defined by visual field (VF) deterioration, while structural progression was characterized by thinning of the retinal nerve fiber layer (RNFL) or ganglion cell inner plexiform layer (GCIPL).

Results. Among 84 participants (mean age, 60.5 years; mean deviation, −5.01 decibels [dB]) with newly diagnosed NTG followed for an average of 69.7 months, 63.1% progressed during the observation period. Specifically, 29.8% progressed by VF, and 48.8% progressed by either RNFL or GCIPL. In Cox proportional hazards analysis, disc hemorrhage (hazard ratio [HR], 2.82; 95% confidence interval [CI], 1.48–5.35), female gender (HR, 1.98; 95% CI, 1.08–3.62), and mean IOP during the follow-up period (HR, 1.14 per mm Hg; 95% CI, 1.00–1.31) were significant predictors of glaucomatous progression. Additionally, longer axial length (AL; HR, 0.57 per millimeter; 95% CI, 0.35–0.94) was protective against VF progression faster than −0.50 dB/y, and higher minimum diastolic blood pressure (DBP; HR, 0.96 per mm Hg; 95% CI, 0.92–1.00) was protective against structural progression.

Conclusions. Nearly two-thirds of untreated Chinese patients with NTG progressed over an average follow-up of 70 months by VF, RNFL, or GCIPL. Disc hemorrhage, female gender, higher mean IOP, shorter AL, and lower minimum DBP were significant predictors for disease progression.

Keywords: normal-tension glaucoma, natural history, progression, risk factors

Glaucoma, a chronic and progressive optic neuropathy, is a leading cause of irreversible blindness worldwide.[1,2] Elevated IOP is commonly recognized as a significant and independent risk factor for glaucoma.[3] However, most individuals diagnosed with primary open-angle glaucoma (POAG) have IOP levels within the normal range, referred to as normal-tension glaucoma (NTG), even more commonly among Asian populations.[4,5] Previous studies have indicated that over 80% of patients in China were diagnosed with NTG.[6,7]

It appears that, without treatment, disease progression among these patients with NTG tends to be gradual. In the Collaborative Normal-Tension Glaucoma Study (CNTGS), approximately one-third of untreated patients experienced localized progression within a 3-year time frame, increasing to 50% within 5 to 7 years.[8] Findings from the Early Manifest Glaucoma Trial (EMGT) indicated that 56% of patients with untreated NTG progressed progression during the 6-year follow-up.[9] Nevertheless, there remains a dearth of prospective data on the natural course of NTG in the Chinese population.

To fill this gap, we conducted a prospective observational cohort study of Chinese patients with newly diagnosed NTG. The aim was to investigate the natural progression of untreated NTG and identify factors associated with glaucomatous progression.

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Methods

The Wenzhou Glaucoma Progression Study (WGPS), a prospective longitudinal cohort study conducted at the Eye Hospital of Wenzhou Medical University, was designed to examine the natural progression of NTG in Chinese patients and investigate the characteristics and potential risk factors associated with disease progression. Participants were recruited prospectively from a community-based screening program and among eligible outpatients newly diagnosed in hospital clinics. This study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University (No. KYK-2013-12). Written informed consent was obtained from each study participant at the time of enrollment after a full explanation of the study.

Definitions

NTG was defined as follows:[10] (1) open anterior chamber angles confirmed by gonioscopy; (2) median untreated IOP readings less than 21 mm Hg on six separate occasions, with no single reading more than 24 mm Hg; (3) the presence of glaucomatous optic neuropathy based on disc photographs (vertical cup/disc ratio [VCDR] >0.7, VCDR asymmetry >0.2, or neural rim tissue <0.1, or localized or diffuse retinal nerve fiber layer [RNFL] defects on fundus photography); and (4) two or more repeatable and corresponding glaucomatous visual field defects (GVFs) at baseline. The criteria for defining GVFs are met when any of the following conditions were satisfied:[11] (1) Glaucoma Hemifield Test results outside normal limits, (2) pattern standard deviation with a P value <0.05, and (3) three or more contiguous points depressed with a probability P value <5% and at least 1 point with a probability P value <1% in the pattern deviation plot.

Glaucoma progression by visual field (VF) was determined using the guided progression analysis provided in the FORUM Glaucoma Workplace (software version 4.2; Carl Zeiss Meditec AG, Jena, Germany). VF progression was defined according to EMGT criteria: three or more of the same points showed significant deterioration in VF sensitivity compared to baseline for three consecutive reliable VF examinations.[12] Reliable VF tests required false negatives <15%, false positives <15%, and fixation losses <20%. Progressive thinning of the RNFL or ganglion cell plexiform layer (GCIPL) was defined as a consistent presence of significant thickness variations in 20 or more adjacent superpixels (1 superpixel = 4 × 4 pixels) on the thickness map, excluding the peripapillary atrophy area if present, when compared to baseline examinations. These variations exceed the inherent superpixel location variability observed in test–retest results during successive follow-up visits.[13] All spectral-domain optical coherence tomography (SD-OCT) scan images underwent a meticulous manual quality review, following a standardized protocol established by the Imaging Data Evaluation and Analysis Reading Center.[14] Only good-quality OCT measurements were used, defined as images with scan quality ≥6/10 and without poor clarity, blink artifacts, local weak signal, segmentation failure, or distinct media opacities.

Clinical Assessment

After enrollment, comprehensive ophthalmologic assessments were performed, including presenting visual acuity (VA), autorefraction (Nidek ARK-510A Autorefractometer; NIDEK Co. Ltd, Tokyo, Japan), VF tests with standard automated perimetry (Humphrey750i, SITA 24–2 Standard; Zeiss, Oberkochen, Germany), SD-OCT (Cirrus HD-OCT 4000/5000; Zeiss, Oberkochen, Germany) and dilated fundus photography (Visucam 200; Zeiss), IOP using Goldmann applanation tonometry (HAAG-STREIT 900 CM; Haag-Streit, Kloniz, Switzerland), and slit-lamp examination. Axial length (AL) and central corneal thickness (CCT) were measured using a noncontact biometer (Lenstar 900; Haag-Streit) once a year. The SD-OCT examinations, VF tests, and IOP measurements were performed every 3 months. During each evaluation, IOP was measured twice, and if the two measurements differed by more than 2 mm Hg, a third measurement was taken. The mean of two or the median of three IOP measurements was used in analyses.

Patients completed self-reported questionnaires, including information on medical conditions, smoking habits (classified as never smoked, current smoking, former smoker, or passive smoker), alcohol consumption, and demographic variables. Current smoking was defined as those actively smoking or having quit within the preceding 3 months. Meanwhile, ongoing alcohol intake was determined by any amount of recorded alcohol consumption within the prior year. Furthermore, each visit included measurements for blood pressure (BP). Two seated BP measurements were taken consecutively from both arms, following a minimum of 5 minutes of rest in a calm environment. A digital sphygmomanometer (Hem-8102A; OMRON, Dalian, China) was utilized for the readings. Participants ensured their bladder was empty and refrained from smoking, engaging in physical activity, and consuming caffeinated beverages for at least 30 minutes before measurements. The results from both arms were then averaged to determine the mean systolic BP (SBP) and diastolic BP (DBP) for each visit.

The presence of disc hemorrhage (DH) was defined as the presence of DH detected on the disc photographs taken during the follow-up period. Mean IOP, SBP, and DBP were computed by averaging all the measurements obtained during the follow-up period. Fluctuations in IOP, SBP, and DBP were quantified using their respective SDs, based on the measurements. Maximum and minimum SBP or DBP represented the highest and lowest single measurement recorded throughout the follow-up, respectively.

Patients with confirmed VF progression during the follow-up period were prescribed topical IOP-lowering eye drops immediately. Although follow-up data were continued after this intervention, information regarding structural progression was censored from the time of functional progression onward. Subsequent follow-up data were excluded from analysis in this study.

Participant Selection

Inclusion criteria included (1) 18 years of age or older at baseline and (2) had been subjected to more than four good-quality OCT and five reliable VF measurements (after excluding the first VF test) during the follow-up period. Patients were excluded if they presented any other ocular diseases or systemic diseases that potentially caused lesions in the optic nerve or visual function impairment.

In cases where patients had bilateral NTG, the eye with VF progression was included if unilateral VF progression was observed. If both eyes were eligible for inclusion, with

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or without VF progression, one eye was randomly selected for the study.

Sample Size

According to the guidelines for determining the sample size for Cox regression modeling, it is advisable to ensure a minimum of 10 positive events per variable to maintain adequate statistical power. In the context of three prognostic factors linked to the risk of visual field damage progression in NTG (disc hemorrhage, sex, myopic refractive error),[15] a minimum of 30 positive events is deemed necessary. Consequently, in order to meet this criterion, the CNTGS found that approximately half of the untreated patients had progressed by VF within 5 to 7 years,[8] and a sample size of 60 participants was considered essential in the present study and achieved.

Statistical Analysis

All statistical analyses and data visualization were performed using R statistical software version 4.1.3 (R Project for Statistical Computing, Vienna, Austria). Data are presented as *n* (%) for categorical variables and mean ± SD for continuous variables. Subsequently, univariate and multivariable Cox proportional hazards models were employed to identify potential risk factors for glaucoma development.

The study assessed the effects of demographic characteristics such as age and gender; baseline factors including IOP, CCT, spherical equivalent, AL, and perimetric mean deviation (MD); and follow-up factors such as follow-up IOP and BP. The presence of DH and self-reported medical histories of hypertension, diabetes, smoking, and alcohol consumption were also evaluated. Factors with $P < 0.2$ in the univariate analysis were included in multivariable models using a multivariable backward stepwise regression approach based on the minimum Akaike information criteria. To address multicollinearity, variables with a variance inflation factor exceeding 2.0 were excluded. Time from baseline to progression was assessed using the Kaplan–Meier log-rank test.

Results

The analysis in this study was centered on patients who met the specified inclusion criteria from the WGPS cohort (Supplementary Fig. S1). Initially, eligibility was assessed for 223 patients and 322 eyes with NTG from the WGPS. Among them, 76 eyes had a follow-up duration of less than 2 years, and 91 eyes were excluded due to receiving IOP-lowering treatment. Additionally, 46 eyes lacked a sufficient number of reliable examinations and 25 participants had both eyes eligible. Ultimately, this study included a total of 84 eyes from 84 patients with untreated NTG, with a mean age of 60.5 ± 10.7 years, and 45 (53.6%) were female (Table 1). The mean IOP and MD at baseline were 14.86 ± 2.95 mm Hg and −5.01 ± 3.59 decibels (dB), respectively. The mean follow-up duration for NTG eyes was 69.7 ± 20.9 months, and the mean number of VF tests conducted was 11.1 ± 4.6, with 57 patients (67.9%) having 60 or more months of follow-up.

Fifty-three eyes (63.1%) progressed by either VF or OCT with a median survival time of 53.0 months (95% confidence interval [CI], 46.0–67.0 months, Fig. C). Twenty-five eyes (29.8%) progressed by VF (median rate of deterioration −0.30 dB/y; interquartile range, −0.65 to −0.20 dB/y), including 12 (14.3%) who progressed faster than −0.50 dB/y. Structural progression (RNFL/GCIPL progression) was detected in 41 patients (48.8%), including 15 patients (17.9%) for only RNFL progression, 6 patients

Table 1. Comparisons of Demographics and Ocular Characteristics in Patients With NTG Between Progressive and Nonprogressive Group (based on VF or GCIPL/RNFL Progression)

Characteristic	Total ($N = 84$)	Progression ($n = 53$)	Nonprogression ($n = 31$)	*P* Value
Age at baseline, y	60.5 ± 10.7	61.2 ± 10.5	59.3 ± 11.4	0.150
Gender, female	45 (53.6)	35 (66.0)	10 (32.3)	**0.003**
Baseline IOP, mm Hg	14.86 ± 2.95	15.25 ± 2.84	14.19 ± 3.05	**0.040**
Baseline MD, dB	−5.01 ± 3.59	−4.94 ± 3.16	−5.12 ± 4.29	0.846
CCT, µm	542.64 ± 32.34	536.85 ± 31.41	552.87 ± 31.92	0.051
AL, mm	24.20 ± 1.57	24.20 ± 1.56	24.19 ± 1.61	0.996
Presenting VA, logMAR	0.19 ± 0.19	0.22 ± 0.21	0.13 ± 0.16	**0.033**
SE, D	−1.00 ± 3.07	−0.94 ± 2.94	−1.11 ± 3.33	0.770
Mean IOP, mm Hg	14.57 ± 2.15	14.90 ± 2.09	14.00 ± 2.17	0.065
IOP fluctuation, mm Hg	1.78 ± 0.49	1.87 ± 0.50	1.63 ± 0.46	**0.035**
Diabetes	15 (17.9)	10 (18.9)	5 (16.1)	0.772
Hypertension	35 (41.7)	19 (35.8)	16 (51.6)	0.157
Current smoking	14 (16.7)	9 (17.0)	5 (16.1)	0.717
History of alcohol	56 (66.7)	34 (64.2)	22 (71.0)	0.531
History of DH	18 (21.4)	16 (30.2)	2 (6.5)	**0.011**
Mean SBP, mm Hg	126.8 ± 14.0	125.5 ± 14.1	129.0 ± 13.9	0.241
Minimum SBP, mm Hg	113.1 ± 13.0	111.5 ± 12.5	115.8 ± 13.5	0.241
Maximum SBP, mm Hg	141.7 ± 16.7	140.6 ± 16.6	143.5 ± 16.9	0.330
SBP fluctuation, mm Hg	8.7 ± 3.0	8.7 ± 2.8	8.8 ± 3.3	0.872
Mean DBP, mm Hg	73.9 ± 7.6	72.3 ± 7.1	76.6 ± 7.8	**0.019**
Minimum DBP, mm Hg	63.4 ± 8.8	61.1 ± 8.3	67.2 ± 8.4	**0.004**
Maximum DBP, mm Hg	84.3 ± 8.9	83.3 ± 9.3	86.2 ± 7.9	0.069
DBP fluctuation, mm Hg	6.4 ± 1.9	6.7 ± 2.0	6.0 ± 1.7	0.100

Values are presented as number (%) or mean ± SD. Significant *P* values are shown in bold type. D, diopters; SE, spherical equivalent.

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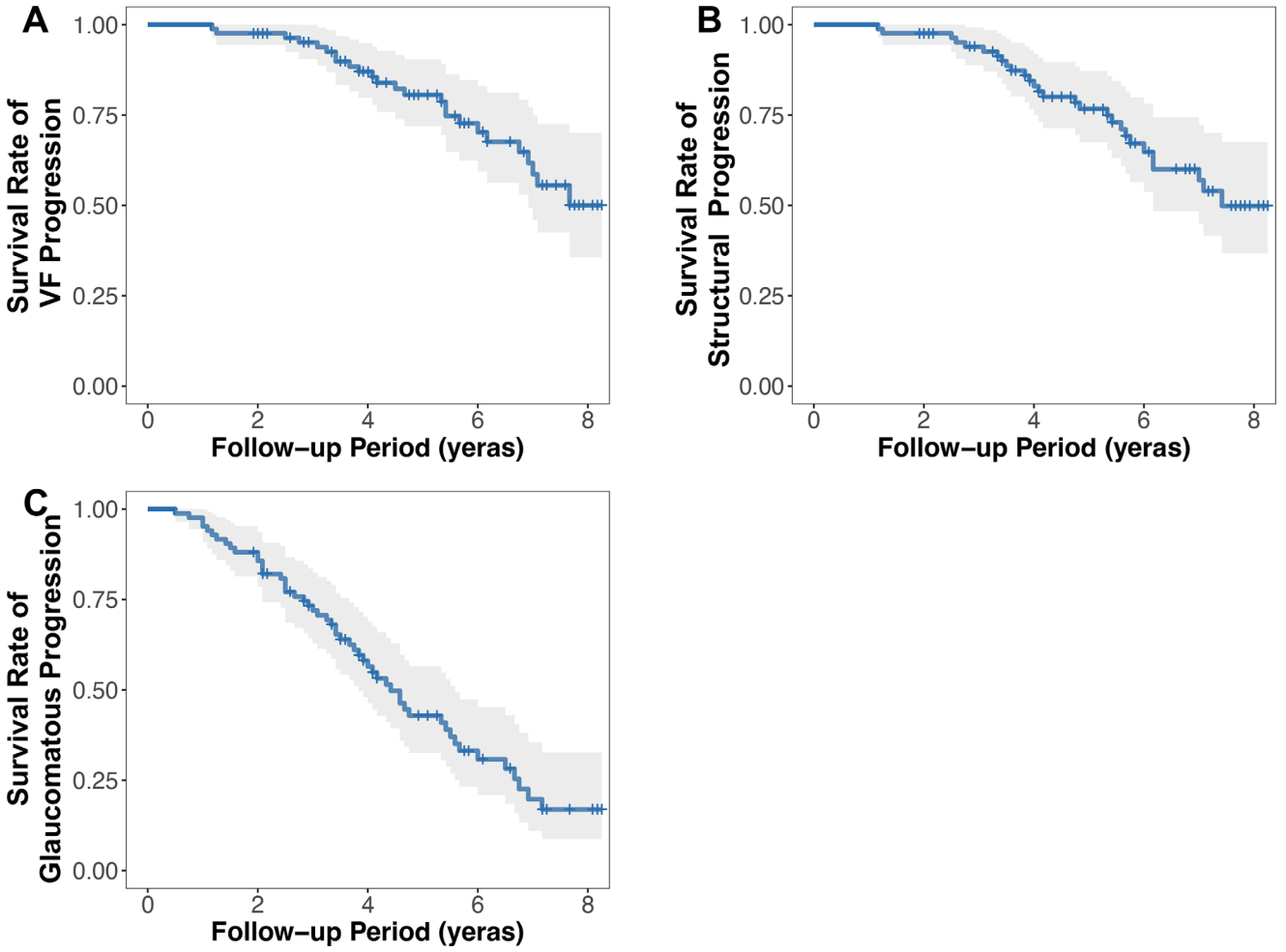

Figure. Kaplan–Meier survival curve with 95% confidence interval according to time from baseline. (**A**) Kaplan–Meier survival analysis based on VF progression. (**B**) Kaplan–Meier survival analysis based on RNFL/GCIPL progression. (**C**) Kaplan–Meier survival analysis based on glaucomatous progression.

(7.1%) for only GCIPL progression, and 20 patients (23.8%) for both. The mean time to progression for functional and structural changes was 55.3 ± 21.7 months and 41.2 ± 21.8 months, respectively. Using survival analysis, at 60 months, 19.4% (95% CI, 9.6–28.1%) progressed by VF and 48.5% (95% CI, 34.1%–59.7%) by structural criteria, with 57.1% (95% CI, 43.5%–67.4%) progressing by either VF or OCT (Fig.).

Risk Factors for Progression

Table 1 compares clinical demographics and ocular characteristics between the progressive and nonprogressive groups, based on VF or GCIPL/RNFL progression. The progressive group had higher baseline IOP, worse VA, and larger IOP fluctuation during the follow-up period compared to the nonprogressive group ($P = 0.040$, $P = 0.033$ and $P = 0.035$, respectively) and lower mean DBP and minimum DBP ($P = 0.019$ and $P = 0.004$, respectively). Furthermore, the progressive group had a significantly higher proportion of female participants (66.0% vs. 32.3%, $P = 0.003$) and DH occurrence (30.2% vs. 6.5%, $P = 0.011$).

In the Cox proportional hazards models, the presence of DH (model 1: hazard ratio [HR], 3.10; 95% CI, 1.34–7.18; $P = 0.008$; model 2: HR, 2.86; 95% CI, 1.25–6.55; $P = 0.013$), higher baseline IOP (HR, 1.23 per mm Hg; 95% CI, 1.07–1.41; $P = 0.003$), and mean IOP during the follow-up period (HR, 1.30 per mm Hg; 95% CI, 1.04–1.64; $P = 0.024$) were significant predictors of VF progression (Table 2). DH (HR, 2.82; 95% CI, 1.29–6.18; $P = 0.010$) and higher mean IOP (HR, 1.21 per mm Hg; 95% CI, 1.02–1.43; $P = 0.025$) were also significantly associated with structural progression (GCIPL/RNFL progression) in patients with NTG, while older age (HR, 0.97 per year; 95% CI, 0.97–0.99; $P = 0.012$) and higher minimum DBP (HR, 0.96 per mm Hg; 95% CI, 0.92–1.00; $P = 0.027$) were identified as protective factors (Table 3). Additionally, female gender (model 1: HR, 1.98; 95% CI, 1.08–3.62; $P = 0.027$; model 2: HR, 2.27; 95% CI, 1.27–4.06; $P = 0.006$), DH (model 1: HR, 2.82; 95% CI, 1.48–5.35; $P = 0.002$; model 2: HR, 2.73; 95% CI, 1.44–5.15; $P = 0.002$), and higher mean IOP (HR, 1.14 per mm Hg; 95% CI, 1.00–1.31; $P = 0.051$) were associated with a higher risk of glaucomatous progression (defined as functional or structural progression, Table 4). Current smoking (HR, 4.82; 95% CI, 1.10–21.10; $P = 0.037$) was significantly associated with progressing by VF faster than −0.50 dB/y (Table 5). Longer AL (HR, 0.57 per mm; 95% CI, 0.35–0.94; $P = 0.026$) was protective against this fast progression.

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Table 2. Univariable and Multivariable Cox Analysis of Glaucoma Progression as Determined by VF Defects for Patients With NTG

	Univariate Model			Multivariable Model 1			Multivariable Model 2		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Baseline									
Age, y	1.05	1.01–1.10	0.029	1.05	1.00–1.10	**0.034**	1.06	1.00–1.11	**0.042**
MD, dB	1.03	0.91–1.18	0.614						
IOP, mm Hg	1.22	1.07–1.38	0.003				1.23	1.07–1.41	**0.003**
SE, D	1.16	0.99–1.36	0.061						
AL, mm	0.73	0.55–0.99	0.040						
HM	0.46	0.06–3.40	0.445						
CCT, µm	0.99	0.97–1.00	0.055	0.99	0.97–1.00	**0.030**	0.99	0.97–1.00	**0.032**
Gender (female)	2.00	0.86–4.64	0.107						
Diabetes	0.90	0.31–2.62	0.846						
Hypertension	0.69	0.31–1.57	0.378						
Current smoking	1.31	0.45–3.85	0.618						
History of alcohol	0.88	0.38–2.04	0.757						
History of DH	2.60	1.16–5.86	0.021	3.10	1.34–7.18	**0.008**	2.86	1.25–6.55	**0.013**
Mean IOP, mm Hg	1.26	1.02–1.55	0.030	1.30	1.04–1.64	**0.024**			
IOP fluctuation, mm Hg	0.79	0.32–1.94	0.602						
Mean SBP, mm Hg	1.01	0.99–1.04	0.353						
Minimum SBP, mm Hg	1.02	0.99–1.05	0.196						
Maximum SBP, mm Hg	1.01	0.98–1.03	0.648						
SBP fluctuation, mm Hg	1.00	0.87–1.15	0.992						
Mean DBP, mm Hg	0.99	0.94–1.04	0.683						
Minimum DBP, mm Hg	1.02	0.97–1.07	0.490						
Maximum DBP, mm Hg	0.97	0.92–1.02	0.190						
DBP fluctuation, mm Hg	0.82	0.65–1.05	0.114						

Significant *P* values are shown in bold type. Multivariable model 1: multivariable model containing all statistically significant factors in the univariate analysis except for baseline IOP. Multivariable model 2: multivariable model containing all statistically significant factors in the univariate analysis except for mean IOP during follow-up period. HM, high myopia.

Table 3. Univariable and Multivariable Cox Analysis of Structural Progression (GCIPL/RNFL Progression) for Patients With NTG

	Univariate Model			Multivariable Model		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Baseline						
Age, y	0.97	0.94–1.00	0.044	0.97	0.94–0.99	**0.012**
MD, dB	1.00	0.91–1.10	0.969			
IOP, mm Hg	1.04	0.94–1.16	0.463			
SE, D	0.97	0.88–1.07	0.560			
AL, mm	1.02	0.85–1.23	0.802			
HM	1.71	0.61–4.84	0.311			
CCT, µm	0.99	0.98–1.00	0.036	0.99	0.98–1.00	0.074
Gender (female)	2.05	1.07–3.90	0.030			
Diabetes	1.43	0.66–3.11	0.370			
Hypertension	0.55	0.28–1.05	0.069			
Current smoking	1.13	0.50–2.56	0.778			
History of alcohol	0.98	0.50–1.91	0.943			
History of DH	2.74	1.32–5.66	0.007	2.82	1.29–6.18	**0.010**
Mean IOP, mm Hg	1.11	0.95–1.29	0.193	1.21	1.02–1.43	**0.025**
IOP fluctuation, mm Hg	1.18	0.61–2.29	0.613			
Mean SBP, mm Hg	0.98	0.96–1.01	0.189			
Minimum SBP, mm Hg	0.98	0.95–1.00	0.089			
Maximum SBP, mm Hg	0.98	0.96–1.00	0.106			
SBP fluctuation, mm Hg	0.97	0.87–1.08	0.592			
Mean DBP, mm Hg	0.97	0.93–1.02	0.263			
Minimum DBP, mm Hg	0.97	0.93–1.00	0.086	0.96	0.92–1.00	**0.027**
Maximum DBP, mm Hg	0.98	0.94–1.02	0.261			
DBP fluctuation, mm Hg	1.07	0.91–1.26	0.398			

Significant *P* values are shown in bold type.

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Table 4. Univariable and Multivariable Cox Analysis of Glaucoma Progression (VF/GCIPL/RNFL Progression) for Patients With NTG

	Univariate Model			Multivariable Model 1			Multivariable Model 2		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Baseline									
Age, y	0.99	0.96–1.01	0.300						
MD, dB	1.00	0.93–1.09	0.924						
IOP, mm Hg	1.07	0.98–1.17	0.148						
SE, D	1.01	0.92–1.10	0.880						
AL, mm	0.97	0.82–1.15	0.720						
HM	1.30	0.47–3.61	0.620						
CCT, µm	0.99	0.98–1.00	0.014	0.99	0.98–1.00	0.073			
Gender (female)	2.26	1.27–4.02	0.006	1.98	1.08–3.62	**0.027**	2.27	1.27–4.06	**0.006**
Diabetes	1.39	0.69–2.77	0.356						
Hypertension	0.58	0.33–1.03	0.064				0.62	0.35–1.11	0.110
Current smoking	1.29	0.65–2.58	0.469						
History of alcohol	1.01	0.56–1.82	0.970						
History of DH	2.88	1.53–5.42	0.001	2.82	1.48–5.35	**0.002**	2.73	1.44–5.15	**0.002**
Mean IOP, mm Hg	1.11	0.97–1.27	0.136	1.14	1.00–1.31	0.051			
IOP fluctuation, mm Hg	1.25	0.71–2.23	0.442						
Mean SBP, mm Hg	0.99	0.97–1.01	0.248						
Minimum SBP, mm Hg	0.98	0.96–1.01	0.177						
Maximum SBP, mm Hg	0.99	0.97–1.01	0.162						
SBP fluctuation, mm Hg	0.99	0.90–1.08	0.760						
Mean DBP, mm Hg	0.98	0.94–1.02	0.221						
Minimum DBP, mm Hg	0.98	0.94–1.01	0.148						
Maximum DBP, mm Hg	0.98	0.94–1.01	0.167						
DBP fluctuation, mm Hg	1.03	0.89–1.19	0.672						

Significant *P* values are shown in bold type. Multivariable model 1: multivariable model containing all statistically significant factors in the univariate analysis except for baseline IOP. Multivariable model 2: multivariable model containing all statistically significant factors in the univariate analysis except for mean IOP during follow-up period.

Table 5. Univariable and Multivariable Cox Analysis of Progression Faster Than −0.5 dB per Year for Patients With NTG

	Univariate Model			Multivariable Model 1		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Baseline						
Age, y	1.00	0.95–1.06	0.969			
MD, dB	1.05	0.87–1.26	0.627			
IOP, mm Hg	1.18	0.98–1.42	0.089			
SE, D	1.17	0.93–1.47	0.174			
AL, mm	0.64	0.40–1.02	0.058	0.57	0.35–0.94	**0.026**
HM	0.97	0.12–7.57	0.977			
CCT, µm	0.98	0.96–1.00	0.047			
Gender, female	1.85	0.56–6.13	0.318			
Diabetes	0.96	0.21–4.39	0.958			
Hypertension	1.29	0.41–4.00	0.664			
Current smoking	2.49	0.66–9.46	0.180	4.82	1.10–21.10	**0.037**
History of alcohol	0.70	0.20–2.40	0.565			
History of DH	1.19	0.32–4.44	0.791			
Mean IOP, mm Hg	1.26	0.93–1.70	0.136			
IOP fluctuation, mm Hg	0.74	0.20–2.74	0.647			
Mean SBP, mm Hg	1.03	0.99–1.07	0.204			
Minimum SBP, mm Hg	1.03	0.99–1.07	0.204			
Maximum SBP, mm Hg	1.01	0.97–1.04	0.690			
SBP fluctuation, mm Hg	0.92	0.74–1.14	0.450			
Mean DBP, mm Hg	1.05	0.98–1.13	0.167			
Minimum DBP, mm Hg	1.05	0.98–1.13	0.142			
Maximum DBP, mm Hg	1.01	0.95–1.08	0.669			
DBP fluctuation, mm Hg	0.92	0.66–1.28	0.613			

Significant *P* values are shown in bold type.

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Discussion

We examined the natural course and risk factors for progression of untreated NTG in a cohort of Chinese patients recruited equally from the community and outpatient clinics. Among the 84 eyes studied, nearly two-thirds progressed by either VF or GCIPL/RNFL, with a median survival time of 53 months.

Previous cohort studies have reported varying rates of VF progression in untreated NTG. The CNTGS found that approximately half of untreated patients progressed by VF within 5 to 7 years.[8] The EMGT reported VF progression in 56% of patients with untreated NTG over 6 years,[9] and the Japanese Lower Normal Glaucoma Study found a 50% progression rate at 5 years.[16] Similarly, a study from Hong Kong, China, reported VF progression in 49.7% of patients over a 36-month follow-up period.[10] In comparison to these studies, we had a lower rate of VF progression at 70 months (30%). And it must be noted that the eye with VF progression was included in the study when unilateral VF progression was observed in order to better understand the risk factors associated with disease progression, which would somewhat overestimate the progression rate. So, a relatively slower rate of VF progression in untreated NTG was observed in our study. A cohort study conducted in South Korea reported a similar result to ours, with 24.8% of included patients showing VF progression at 5 years.[17] We hypothesize that the lower rate of VF progression observed in the present study could be attributed to a several factors. In our study, VF tests were conducted at approximately 6-month intervals, whereas the EMGT and the Japanese Lower Normal Glaucoma Study tested more frequently (every 3 months), allowing for more rapid detection of worsening. As previously reported, increased frequency of testing reduces the time needed to detect VF progression.[18] A second explanation is that we identified half our patients from the community, and these individuals may have slower rates of progression. We did not see any difference in that analysis, however.

Rates of progression in our cohort were similar to those previously reported when allowing for either functional or structural progression. The CNTGS reported a progression rate of approximately 60% at 5 years of follow-up (defined as VF or disc progression using photos),[8] and the Japanese Lower Normal Glaucoma Study reported a prevalence of 66% at 5 years (defined as VF or disc/peripapillary retina progression using photos).[16] Our findings highlight the potential underestimation of glaucomatous progression based solely on VF defects in NTG, especially during the early stages of the disease.

In our study, we assessed potential risk factors for NTG progression, including IOP and IOP-independent factors. IOP is the only known modifiable risk factor for glaucomatous progression, even in NTG.[8] Previous studies have consistently supported the significance of mean IOP as a risk factor for glaucoma progression. In our study, mean follow-up IOP was identified as a significant risk factor for both functional and structural progression in NTG, which was also consistent with our previously published results.[19] Furthermore, the CNTGS demonstrated that a 30% reduction in IOP lowered the progression rate from 35% to 12% over a 5-year follow-up period in patients with NTG.[20] Our finding that higher IOP was associated with higher risk of progression and clinical trial data supporting IOP lowering in treating NTG underscore the role of IOP lowering in managing patients with glaucoma even when they have low untreated IOP.

Interestingly, IOP fluctuation was not a significant risk factor for progression in the present study. Others have reported an association between IOP fluctuation and incident glaucoma progression in patients with NTG (mean IOP in these studies, 10.8 – 13.5 mm Hg).[16] Individuals participating in the present study had a higher mean IOP, which may have driven the association and reduced the impact of IOP fluctuation.

Disc hemorrhage, a well-established risk factor for glaucoma progression,[21] was also found to be significantly associated with glaucoma progression in our study. DH increased the risk of glaucomatous progression (defined as VF or RNFL/GCIPL) two to three folds (Supplementary Table S1). Although the exact cause of DH remains unclear, we hypothesize that hemodynamic disturbances play a significant role in the development of glaucomatous DH. These disturbances share some common mechanisms with axonal transport disruption, which is closely related to the progression of glaucomatous damage.[22]

In this study, current smoking was a significant predictor of progression faster than −0.50 dB/y, which is a novel finding in NTG. This finding aligns with recent evidence from a retrospective cohort study.[23] Analysis of data over a median follow-up period of 12.5 years revealed that higher smoking intensity was associated with a faster rate of VF defects (−0.05 dB/y per 10 pack-years). Similarly, Nishida et al.[24] reported that greater smoking intensity was associated with faster RNFL thinning (−0.06 µm/y per 10 pack-years). These findings are likely related to the effects of nicotine and other substances in tobacco, which can diminish blood flow to the optic nerve head and choroid. Several recent studies have shown decreased optic nerve vessel density in smokers, particularly among those with more intensive smoking,[25] providing partial support for smoking being causally related to more rapid progression. In this study, there were only 14 patients with a smoking history. Consequently, we were unable to explore different levels of smoking intensity and the progression of visual field deterioration.

A lower DBP was associated with structural progression in our study. Similar findings have been reported in prior research. A lower minimum DBP was found to be associated with GCIPL progression (HR, 0.964 per mm Hg; 95% CI, 0.930–0.999; $P = 0.022$) in a retrospective cohort study involving 166 patients with NTG.[26] In the Barbados Eye Study, a 10-mm Hg rise in SBP was associated with a 9% reduction in risk of long-term open-angle glaucoma incidence, and analogous outcomes were noted for DBP, pulse pressure, and arterial pressure, all showing relative risk ratio values below 1.[27] Taking into account previous studies that have demonstrated a strong connection between DBP and tissue perfusion,[28] it is reasonable to speculate that DBP may play a crucial role in averting the progression of NTG.

Female gender was associated with a higher likelihood glaucomatous progression. This finding is consistent with previous studies that also reported female gender as a risk factor for glaucoma, such as the CNTGS,[29] involving participants 60 years or older. In our study, the average age of women was 60.6 years, with 95.6% of them being postmenopausal at baseline (data not shown). Previous research has indicated the presence of estrogen receptors in retinal ganglion cells.[30] Furthermore, postmenopausal hormone therapy containing estrogen may reduce the risk of

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POAG according to a retrospective longitudinal cohort study involving 152,163 female participants 50 years or older.[31]

Multivariable Cox regression analysis in our study showed that a longer AL was associated with a reduced likelihood of VF progression faster than −0.50 dB/y. This finding aligns with the observations made by Qiu et al.,[32] in which patients with longer AL tended to have a lower risk of fast VF progression in POAG. One possible explanation for this phenomenon is that as the AL increases, the degree of eyeball deformation in response to each 1-mm Hg elevatation in IOP becomes less pronounced. Moreover, individuals with longer AL experience reduced diurnal and nocturnal fluctuations in IOP.[33] These factors collectively may contribute to less fluctuation in IOP and reduced deformation of the lamina cribrosa. As a result, individuals with longer AL may be less susceptible to developing glaucomatous VF defects over time.

In this study, we found something different from everyone else: a positive association between younger age and an increased risk of structural progression. Most studies have reported that older age is significantly associated with VF progression in POAG.[34] One potential explanation for this phenomenon is the age-related increase in SBP, mean arterial pressure (MAP), and pulse pressure.[35] Elevated SBP, pulse pressure, and arterial pressure have been linked to the progression of glaucoma.[26,27] Notably, an age-related increase in SBP was also observed in our cohort (Supplementary Fig. S2).

The association between myopia and progression in patients with NTG has been a topic of debate. In our study, we did not find a significant impact of myopia on glaucomatous progression, which is consistent with some previous studies.[26] However, it is worth noting that other studies have identified myopia as a risk factor for NTG progression.[36] It is important to consider the characteristics of our study population in interpreting these results. Most of the participants in our study were relatively close to emmetropia, with an average AL of 24.35 mm and a prevalence of high myopia (≤−6.00 D) of less than 10%. We likely lacked the power to identify an association with high myopia and progression, given the size of the cohort and the low prevalence of high myopia.

The present study has several limitations that should be acknowledged. First, the sample size was relatively small, with only 84 participants meeting the strict inclusion criteria. This smaller sample size means that some associations with NTG progression may have been missed. Second, the study population had a relatively mild stage of NTG, as indicated by the average baseline MD of −5.01 ± 3.59 dB, with only 17.9% of eyes having an MD worse than −8.00 dB. Consequently, caution should be exercised in generalizing the findings of this study to more severe stages of NTG. Third, certain risk factors that have been the focus of previous studies, such as a history of migraine or a family history of glaucoma, were not evaluated in our current study due to a substantial number of missing data points at baseline.

In conclusion, this study sheds light on the natural progression of NTG in Chinese patients. The findings highlight that a substantial proportion of patients demonstrated functional or structural progression over a 70-month follow-up period. Several factors, including the presence of DH, higher baseline IOP, higher mean IOP, shorter AL, and lower DBP, were identified as potential risk factors for disease progression. Our findings support studies in non-Chinese patients that have shown that IOP-lowering therapy should slow the rate of progression in patients with NTG.

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