Baseline Clinical Characteristics and Patterns of Visual Field Defect in Primary Open-Angle Glaucoma: Comparison Between High-Tension and Normal-Tension Glaucoma in LiGHT China

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Abstract:

Purpose:

To compare the baseline clinical characteristics and patterns of visual field defects between high-tension glaucoma (HTG) and normal-tension glaucoma (NTG) in the Laser in Glaucoma and Ocular Hypertension (LiGHT) China subjects.

Methods:

1105 open-angle glaucoma (OAG) eyes of XXX subjects were enrolled in the LiGHT China cohort were defined as NTG (n=559) and HTG (n=546) according to baseline intraocular pressure (IOP) . The baseline results of visual field tests were classified into pre-perimetric, mild, moderate and severe stages using Hodapp-Parrish-Anderson(HPA) criteria. The mean values of total deviation of the Glaucoma Hemifield Test (GHT) regions and the mean regional hemifield-difference values were calculated. The clinical parameters and VF parameters between NTG and HTG were compared. Clinical factors and VF parameters associated with NTG were identified by logistic regression analysis.

Results:

NTG patients were older, more likely to be female hypertensive and suffer ischemic heart disease than HTG patients (P<0.05 for all comparisons). NTG eyes had thinner central corneal thickness (CCT) than HTG eyes (529.82±32.90mm vs 542.49±32.99mm, P<0.001). HTG and NTG showed similar mean deviation (MD) overall (-4.85±3.89dB vs -4.97±3.60dB, P=0.630) and for each severity group (P>0.05 for all comparisons). As severity increased, NTG and HTG both showed VF defects that were more severe in the superior than inferior hemifield. However, NTG showed significantly greater hemifield asymmetry than HTG, especially in the central region. The results of the multivariable logistic regression analysis demonstrated that thinner CCT, older age, female gender, lower diastolic blood pressure, and greater central hemifield asymmetry were associated with NTG in all OAG.

Conclusions:

In the Light-China trial, NTG and HTG showed similar VF defects at enrollment. NTG and HTG showed worse defects in superior regions as severity increased, however, clinical charateristics and patterns of VF defects were different between the two groups suggesting that there might be differences in the pathophysiological mechanisms of ganglion cell damage NTG and HTG in Chinese patients.

Introduction

Open-angle glaucoma(OAG) is a leading cause of irreversible vision loss worldwide. Although elevated intraocular pressure(IOP) is a risk factor for glaucoma progression, some patients have similar clinical changes with low or normal IOP. OAG can be classified as normal-tension glaucoma(NTG) and high-tension glaucoma(HTG) according to the baseline IOP level. In Asian populations, NTG is the predominant types, with prevalence rates reported as 77% to 92%[1-4].

There has been a long debate regarding the pathogenesis of NTG. It can interpreted as a nerve made vulnerable to IOP in the statistically normal range by a variable mix of a number of other non-pressure risk factors such as vascular inefficiency[8], structural weakness of ocular tissues[9,10], and autonomic [11,12], or mitochondrial dysfunction . Nonetheless, reduction of IOP has proved effective at reducing further nerve damage [5,6,7]. The differences in clinical characteristics and visual field defect may shed light on the underlying pathophysiological mecahnisms in NTG and HTG.

In previous comparative studies of VF defects in NTG and HTG, HTG has shown more diffuse damage, with NTG tending to have localized VF defect closer to fixation[13-15]. Some studies suggested that NTG showed more asymmetric VF defects than HTG[16-18], while others found no significant difference in VF between NTG and HTG[19,20]. Most of the studies had small populations, limited clinical data or were subject to ascertainment bias. Thus, we undertook further comparative analysis of VF patterns in a large cohort of newly diagnosed patients to explore differences between patterns of VF loss in NTG and HTG.

In previous natural history studies of OAG, NTG and HTG showed different clinical characteristics. In EMGT, HTG showed faster progression than NTG [21]. It seemed that higher IOP might accelerate the natural progression of OAG before or without treatment. It was also confirmed, in UKGTS, that the better visual field of OAG eyes had lower baseline IOP than the worse visual field at the initial assessment[22]. Some studies also showed correlation between higher IOP and worse visual filed damage in NTG[23,24], while others did not find that correlation[25].

LiGHT-China is a prospective, single center, randomized treatment trial aiming to investigate the effect of SLT as the initial treatment in OAG/ocular hypertension in a Chinese population[26]. LiGHT-China adopted a protocol similar to LiGHT-UK to facilitate comparisons, although there are some differences, for example almost 50% of LiGHT-China had resenting IOP in the normal range, [27,28] while LiGHT-UK had only 25% patients with NTG.

All of the OAG patients enrolled in our cohort were newly diagnosed without any prior treatment and with no IOP-based enrolment criteria. Differences between the NTG and HTG populations may therefore be representative of the nature of newly diagnosed OAG in China, and thus we aimed to assess the difference of baseline characteristics and visual field patterns in this sample.

Methods

Subjects

All of the OAG (622 patients) for this study were enrolled in the LiGHT-China cohort, which aimed to compare eye drops vs selective laser trabeculoplasty (SLT) as the first-line

treatment for newly diagnosed patients with OAG or OHT[26]. According to the design of the LiGHT-China, all of participants were newly diagnosed with POAG or OHT aged 18 years or older without previous treatment. The exclusion criteria involved visual acuity worse than 6/36 in a study eye, visually significant cataract, history of retinal ischaemia, macular edema, diabetic retinopathy, age-related macular degeneration with neovascularisation or geographic atrophy, previous ocular surgery and contraindication for SLT. Written informed consent was obtained from all participants.

The baseline measurement

At the baseline assessment, patients underwent visual acuity testing (ETDRS logMAR), slit lamp examination, automated VF testing (Humphrey field analyser (HFA) Mark II SITA standard 30–2), IOP measurement (Goldmann applanation tonometry), central corneal thickness (CCT) measurement (Type A ultrasound) and dark room gonisoscopy. The more accurate of the first two VF tests was selected as the baseline VF result for eligible eyes to account for the learning effect. We classified OAG patients into NTG (baseline IOP<21mmHg) and HTG (baseline IOP≥21mmHg).

Analysis of VF Defects

We applied Hodapp-Parrish-Anderson(HPA)[29] guidelines to classify the severity of the HFA tests. The minimum criteria for defective glaucomatous damage was defined as a Glaucoma Hemifield Test outside normal limits on at least two fields, or a cluster of three or more non-edge points in a location typical for glaucoma, all of which are depressed on the pattern deviation plot at a p<5% level and one of which is depressed at a p<1% level on two consecutive fields. The eyes with VF results that do not meet the minimum criteria were classified as pre-perimetric. The severe stage was defined as MD greater than -12 dB, at least one point in the central 5° with a sensitivity of 0 dB, points within the central 5° with sensitivity < 15 dB in both hemifields, more than 50% of the points depressed below the 5% level, or more than 20 points depressed below the 1% level on the pattern deviation plot.

According to the Glaucoma Hemifield Test (GHT)[30] map, the 44 locations of the 30-2 HFA were divided into 5 superior hemifields regions (nasal, central, paracentral, arcuate 1, and arcuate 2) and 5 inferior hemifields coinciding regions. The mean total deviation (mTD) values of each region were calculated.

Statistical analysis

A Student t test for continuous variables and a $\chi 2$ test for categorical variables were performed to compare the characteristics of the clinical and demographic parameters between the NTG and HTG groups.

In order to show the asymmetricity of visual fields, regional differences were defined calculated as that mTD values of superior region superior regional mean TD minus the corresponding inferior regional mean TD mTD values of the inferior corresponding region, and plotted on the GHT maps.

In addition, univariable and multivariable logistic regression analysis was performed to investigate what baseline whether demographic and clinical parameters except baseline IOP and VF parameters were associated with NTG eyes among eyes with OAG.

All statistical analyses were performed using IBM SPSS Statistics (version 25.0 for Windows). All *P* values were two sided and were considered statistically significant when *P*<0.05.

Results:

Table1: Baseline clinical characteristics of OAG patients(N=622)

		OAG(%)	HTG(%)	NTG(%)	P
Total number		622	305	317	
Affected Eyes					0.423$
	unilateral	139(22.3)	64(21.0)	75(23.7)	
	bilateral	483(77.7)	241(79.0)	242(76.3)	
Eligibility					0.563$
	right	61(9.8)	26(8.5)	35(11.0)	
	left	78(12.5)	38(12.5)	40(12.6)	
	bilateral	483(77.7)	241(79.0)	242(76.3)	
Gender					<0.001$
	Male	364(58.5)	202(66.2)	162(51.1)	
	Female	258(41.5)	103(33.8)	155(48.9)	
Age		49.79±17.18	46.71±16.77	52.69±17.10	<0.001*
Blood pressure					
	Systolic blood pressure	128.67± 17.20	129.50± 17.48	127.87± 16.92	0.237*
	Diastolic blood pressure	78.77±9.52	79.53±9.56	78.01±9.43	0.012*
General health					-
	Asthma	6(1.0)	4(1.3)	2(0.6)	0.647$
	Hypertension	111(17.8)	43(14.1)	68(21.5)	0.017$
	Diabetes	30(4.8)	11(3.6)	19(6.0)	0.165$
	Angina	9(1.4)	3(1.0)	6(1.9)	0.540$
	Cardiac arrhythmia	18(2.89)	5(1.6)	13(4.1)	0.067$
	Ischemic heart disease	19(3.1)	5(1.6)	14(4.4)	0.044$
	Migraine	3(0.5)	3(1.0)	0(0)	0.234$
	Stroke	1(0.2)	1(0.3)	0(0)	0.985$
	Blood loss or transfusion	3(0.5)	1(0.3)	2(0.6)	1.000$
Family		69(11.1)	31(10.2)	38(12.0)	0.469$

history of glaucoma	

*Compared by independent *t* test. $Compared by Chi-square test. Values were presented as mean ± SD or number (percentage).

Nearly three quarters of participants in both NTG and HTG had both eyes enrolled. NTG patients were older than HTG patients (52.69±17.10years vs. 46.71±16.77years, *P*<0.001). and more likely to be female (48.9%) than HTG patients (33.8%; (*P*<0.001). The two groups had similar systolic (*P*=0.237) but not diastolic blood pressure (BP), with NTG patients having relatively lower diastolic BP than HTG (*P*=0.012). NTG patients had higher prevalences of hypertension and ischemic heart disease than HTG (*P*<0.05 for both). Hypertension was the most prevalent comorbidity in both NTG (21.5%) and HTG (14.1%). NTG and HTG had similar prevalence of family history of glaucoma (*P*=0.469).

Table 2: Baseline ocular characteristics of OAG eyes(N=1105).

	HTG(n=546)	NTG(n=559)	P
Baseline IOP(mmHg)	24.35±4.61	16.45±2.47	<0.001
CCT(μm)	542.49±32.99	529.82±32.90	<0.001
SE(D)	-3.14±3.82	-2.30±3.82	<0.001
MD(dB)	-4.85±3.89	-4.97±3.60	0.630
PSD	5.02±3.96	5.51±4.04	0.043

Table3: The severity of visual fields of OAG eyes(N=1105) classified by Hodapp-Parrish-Anderson criteria.

		HTG	NTG	P
Preperimetric		167(30.6%)	110(19.7%)	<0.001
Defective		379(69.4%)	449(80.3%)	
	Mild	151(27.7%)	206(36.9%)	0.146*
	Moderate	123(22.5%)	141(25.2%)	
	Severe	105(19.2%)	102(18.2%)	

Compared by Chi-square test. Values were presented as number (percentage).

*Compared in defective visual fields stages: mild, moderate and severe stage.

Table4: Global indices of visual fields of OAG eyes(N=1105) for each severity stage by HPA criteria

	PSD			MD		
	HTG	NTG	P	HTG	NTG	P
Preperimetric	1.67±0.28	1.72±0.31	0.118	-1.40±1.35	-1.59±1.38	0.257
Mild	3.18±1.58	3.48±1.62	0.080	-3.40±1.49	-3.26±1.59	0.423
Moderate	6.76±2.80	7.19±3.15	0.243	-6.49±2.35	-6.40±2.23	0.767
Severe	10.98±2.62	11.38±2.83	0.297	-10.55±2.90	-10.06±3.15	0.245

Compared by independent *t* test. Values were presented as mean ± SD.

HTG eyes had higher baseline IOP (24.35±4.61mmHg), thicker CCT (542.49±32.99um) and higher myopia (-3.14±3.82D) compared with NTG eyes (16.45±2.47mmHg, 529.82±32.90um and -2.30±3.82D) significantly (*P*<0.001 for all comparisons). As was shown in table 2, NTG had similar MD (*P*=0.630) but higher PSD (*P*=0.043) than HTG for total eyes. After classified by HPA criteria in table 4, NTG showed similar MD and PSD as HTG for each severity level (*P*>0.05 for all comparisons). However, HTG eyes had larger proportion of pre-perimetric VF (30.6%) than NTG eyes(19.7%)(*P*<0.001), while NTG and HTG showed similar proportion when compared in the three affected stages(*P*=0.146) in table 3.

Figure 1: Five regions of the superior hemifield and their corresponding locations in the inferior hemifield for the Glaucoma Hemifield Test.

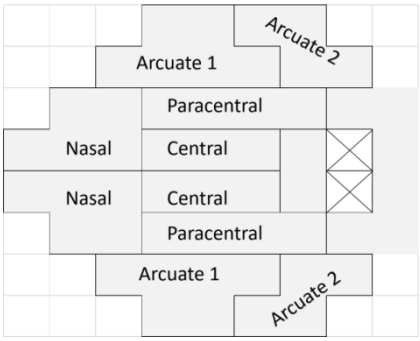


Figure 2: The gray scale maps of mean deviation for each GHT region for each severity level(preperimetric, mild, moderate and severe) of NTG and HTG eyes.

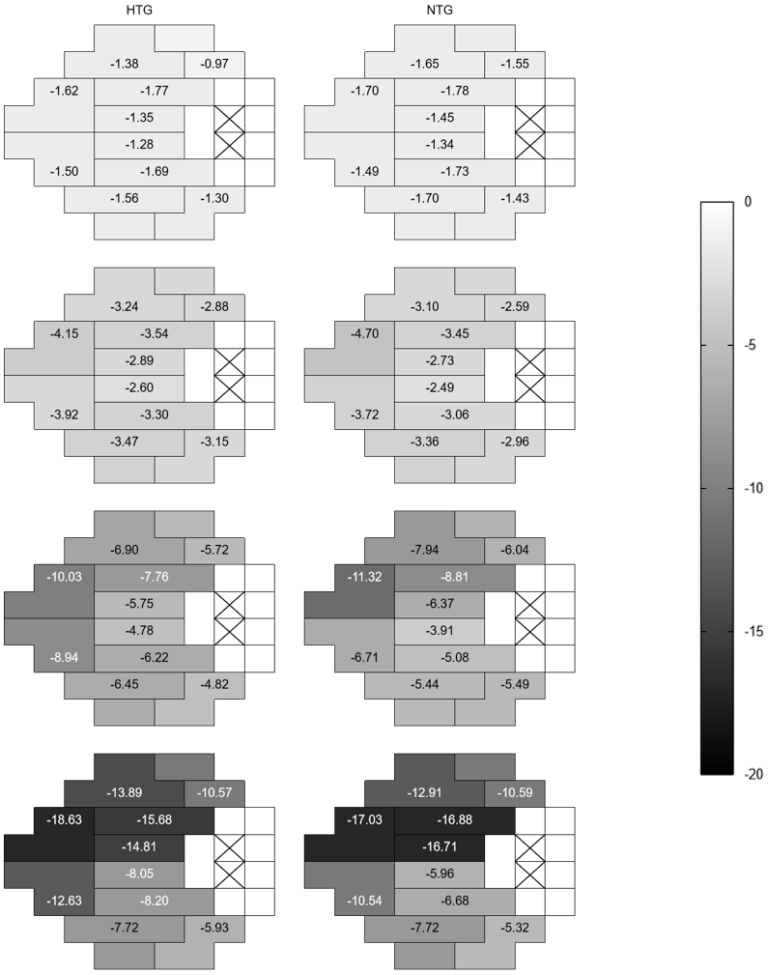


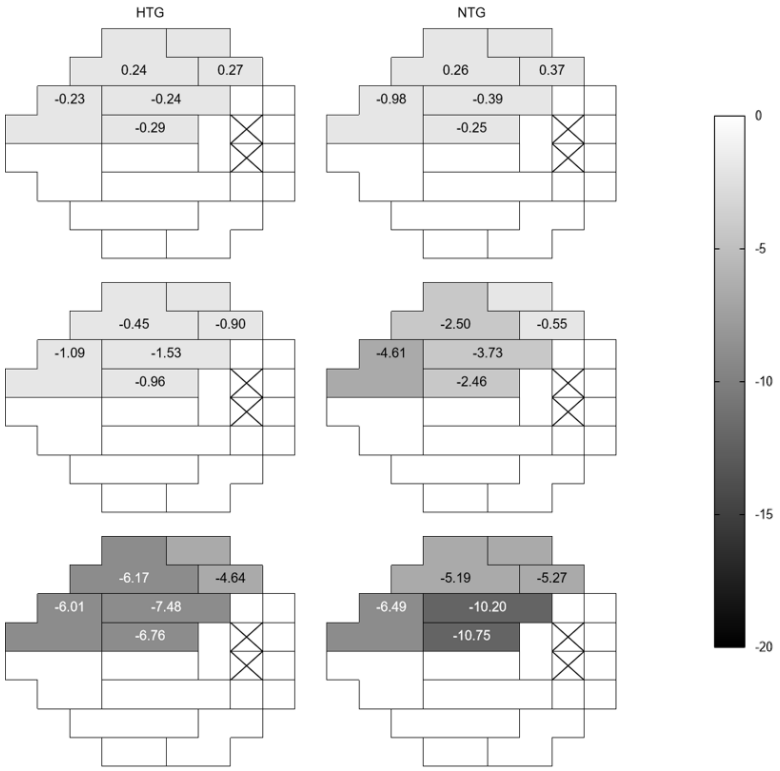
Table 5: The mean deviations for each GHT region of NTG(n=546) and HTG eyes(n=559) for each severity stage and total numbers

	Preperimetric			Mild			Moderate			Severe			Total		
	HTG	**NTG**	**P**	**HTG**	**NTG**	**P**	**HTG**	**NTG**	**P**	**HTG**	**NTG**	**P**	**HTG**	**NTG**	**P**
Hemifield															
Superior	-1.42±1.56	-1.63±1.44	0.259	-3.35±1.95	-3.31±2.04	0.860	-6.99±4.1	-7.85±4.54	0.110	-13.9±6.63	-13.86±6.71	0.964	-5.57±5.85	-6.05±5.83	0.179
Inferior	-1.52±1.5	-1.62±1.39	0.574	-3.55±1.7	-3.27±1.76	0.138	-6.26±3.48	-5.51±3.34	0.078	-8.27±4.62	-7.21±5.57	0.135	-4.42±3.82	-4.22±3.7	0.378
P	0.073	0.885		0.218	0.791		0.166	<0.001		<0.001	<0.001		<0.001	<0.001	
Arcuate1 Region															
Superior	-1.38±1.82	-1.65±1.68	0.214	-3.24±2.3	-3.1±2.58	0.591	-6.9±5.11	-7.94±5.91	0.135	-13.89±9.32	-12.91±9.23	0.448	-5.51±6.73	-5.82±6.62	0.446
Inferior	-1.56±1.65	-1.7±1.53	0.455	-3.47±2.01	-3.36±2.49	0.641	-6.45±4.56	-5.44±4.21	0.063	-7.72±6.15	-7.72±7.64	0.997	-4.35±4.42	-4.35±4.68	0.992
P	0.065	0.691		0.248	0.236		0.512	<0.001		<0.001	<0.001		<0.001	<0.001	
Arcuate2 Region															
Superior	-0.97±1.95	-1.55±1.97	0.017	-2.88±2.65	-2.59±2.71	0.312	-5.72±5.36	-6.04±5.43	0.636	-10.57±8.43	-10.59±8.98	0.989	-4.39±5.91	-4.71±6	0.366
Inferior	-1.3±1.7	-1.43±1.57	0.516	-3.15±2.85	-2.96±2.51	0.510	-4.82±4.49	-5.49±6.31	0.328	-5.93±5.58	-5.32±5.65	0.437	-3.48±4.06	-3.72±4.58	0.354
P	0.004	0.440		0.364	0.091		0.148	0.461		<0.001	<0.001		<0.001	<0.001	
Nasal Region															
Superior	-1.62±1.78	-1.7±1.61	0.702	-4.15±3.39	-4.7±4.32	0.193	-10.03±7.35	-11.32±9.24	0.217	-18.63±9.54	-17.03±9.82	0.234	-7.44±8.5	-8.02±8.7	0.263
Inferior	-1.5±1.69	-1.49±1.63	0.942	-3.92±3.43	-3.72±2.87	0.537	-8.94±6.79	-6.71±5.48	0.004	-12.63±8.51	-10.54±9.47	0.097	-5.95±6.77	-5.28±6.06	0.081
P	0.175	0.063		0.510	0.003		0.238	<0.001		<0.001	<0.001		<0.001	<0.001	
Paracentral Region															
Superior	-1.77±1.65	-1.78±1.51	0.950	-3.54±2.15	-3.45±2.41	0.721	-7.76±6.44	-8.81±7.54	0.229	-15.68±9.38	-16.88±10.38	0.383	-6.24±7.33	-6.92±8.08	0.144
Inferior	-1.69±1.53	-1.73±1.57	0.811	-3.3±1.69	-3.06±2.59	0.324	-6.22±4.44	-5.08±4.35	0.038	-8.2±6.32	-6.68±6.58	0.092	-4.39±4.42	-3.97±4.3	0.111
P	0.338	0.672		0.131	0.061		0.044	<0.001		<0.001	<0.001		<0.001	<0.001	
Central Region															

Superior	-1.35±1.54	-1.45±1.4	0.582	-2.89±2.01	-2.73±2.08	0.468	-5.75±4.26	-6.37±4.95	0.280	-14.81±9.14	-16.71±8.9	0.132	-5.32±6.74	-5.96±7.2	0.130
Inferior	-1.28±1.55	-1.34±1.5	0.754	-2.6±1.9	-2.49±2.09	0.600	-4.78±3.99	-3.91±2.97	0.047	-8.05±5.88	-5.96±5.44	0.009	-3.72±4.22	-3.25±3.47	0.047
P	0.294	0.158		0.016	0.083		0.045	<0.001		<0.001	<0.001		<0.001	<0.001	

From figure 2, HTG and HTG both showed worse defects in superior hemifield than inferior hemifield as the severity of VF increased. As was shown in table 5, NTG and HTG had no more than one region that showed significant hemifield-difference in normal or mild stage. However, four regions of NTG and two regions of HTG in superior hemifield showed worse defects than the corresponding inferior regions for moderate stages. In severe group, all five regions in the superior hemifield showed a deeper average decrease in sensitivity than in the inferior regions in both NTG and HTG. HTG had worse defects than NTG in the inferior nasal region, inferior paracentral region and inferior central region in moderate stage, and inferior central region in the severe group.

Figure3: The gray scale of the hemifield difference of each GHT regions for the three defective VF stages(mild, moderate and severe) of NTG and HTG eyes.



Hemifield difference was defined as superior regional mean MD values minus inferior regional mean MD values.

Figure3 showed the degrees of hemispheric asymmetry in each GHT region across defective VF levels in HTG and NTG groups. There was minor hemifiled difference within 1dB to -1dB in all five regions at mild severity in both NTG and HTG. At moderate VF stage, the difference in all five GHT regions of HTG limited within -2dB, but three regional differences (arctuate1, paracentral and central region) in NTG varied from -2dB to -4dB, especially over -4dB in nasal region. Moreover, at severe VF stage the regional asymmetric differences in HTG and NTG varied from -4dB to -8dB, except the central and paracentral regions of NTG which

were over -10dB.

Table5: The hemifield difference for each GHT regions of NTG and HTG eyes for each defective stage and total defective numbers

	Mild			Moderate			Severe			Total		
	HTG	NTG	P	HTG	NTG	P	HTG	NTG	P	HTG	NTG	P
Hemifield Difference	0.2±1.98	-0.04±2.11	0.280	-0.73±5.8	-2.34±6.44	0.036	-5.63±9.57	-6.65±10.39	0.462	-1.71±6.6	-2.27±6.79	0.235
Arcuate1 Difference	0.24±2.52	0.26±3.17	0.932	-0.45±7.59	-2.5±8.13	0.037	-6.17±12.3	-5.19±13.85	0.589	-1.76±8.37	-1.84±8.57	0.887
Arcuate2 Difference	0.27±3.63	0.37±3.13	0.772	-0.9±6.87	-0.55±8.65	0.717	-4.64±9.6	-5.27±11.13	0.666	-1.47±7.06	-1.21±7.8	0.620
Nasal Difference	-0.23±4.22	-0.98±4.75	0.119	-1.09±10.16	-4.61±11.55	0.010	-6.01±14.16	-6.49±14.34	0.808	-2.1±10.07	-3.36±10.17	0.075
Paracentral Difference	-0.24±1.95	-0.39±2.97	0.588	-1.53±8.35	-3.73±9.36	0.049	-7.48±12.77	-10.2±14.11	0.147	-2.66±8.82	-3.67±9.55	0.116
Central Difference	-0.29±1.47	-0.25±2.02	0.812	-0.96±5.27	-2.46±5.48	0.027	-6.76±11.65	-10.75±10.86	0.012	-2.29±7.4	-3.34±7.44	0.044

As was shown in table 5, there was no significant difference between NTG and HTG for regional asymmetry in mild VF severity among all five regions.(P>0.1 for all comparisons). In the moderate VF severity, NTG had severer asymmetry in paracentral, central, nasal and arcuate1 regions(P<0.05 for all comparisons) than HTG, but the significant difference of asymmetry was only shown in the central region at severe stage(P=0.044).

Table6. Univariable and Multivariable Logistic Regression Analysis of Factors Associated with NTG in 1105 OAG eyes

	Univariable			Multivariable		
	OR	95%CI	P	OR	95%CI	P
SE(per 1D increase)	1.060	1.027 to 1.094	<0.001			
CCT(per 1μm increase)	0.988	0.985 to 0.992	<0.001	0.990	0.986 to 0.994	<0.001
Systolic blood pressure(per 1mmHg increase)	0.996	0.989 to 1.002	0.172			
Diastolic blood pressure(per 1mmHg increase)	0.983	0.971 to 0.994	0.003	0.981	0.969 to 0.993	0.002
Gender(reference:male)	1.827	1.433 to 2.330	<0.001	1.451	1.121 to 1.877	0.005
Age(per year increase)	1.023	1.016 to 1.031	<0.001	1.021	1.013 to 1.028	<0.001
MD(per 1dB increase)	0.992	0.961 to 1.024	0.629			
PSD(per 1 increase)	1.031	1.001 to 1.062	0.043			
Arcuate1 Difference (per -1dB increase)	1.006	0.990 to 1.022	0.483			

Arcuate2 Difference (per -1dB increase)	1.004	0.986 to 1.022	0.681			
Nasal Difference (per -1dB increase)	1.017	1.003 to 1.031	0.015			
Paracentral Difference (per -1dB increase)	1.017	1.002 to 1.033	0.023			
Central Difference (per -1dB increase)	1.026	1.007 to 1.045	0.007	1.022	1.002 to 1.042	0.028

Logistic regression analysis was conducted to identify the parameters associated with NTG , and the dependent variables were coded as follows: 1=eyes with NTG, 0=eyes with HTG.

Table 6. showed the results of logistic regression for analyzing the clinical parameters associated with NTG. In the univariate analysis, NTG eyes were significantly associated with SE (OR=1.060, 95% CI=1.027 to 1.094, and *P<0.001*), CCT (OR=0.988, 95% CI=0.985 to 0.992, and *P<0.001*), diastolic blood pressure (OR=0.983, 95% CI=0.971 to 0.994, and *P=0.003*), female sex (OR=1.827, 95% CI=1.433 to 2.330, and *P<0.001*), age (OR=1.023, 95% CI=1.016 to 1.031, and *P<0.001*), PSD (OR=1.031, 95% CI=1.001 to 1.062, and *P=0.043*), nasal difference (OR=1.017, 95% CI=1.003 to 1.031, and *P=0.015*), paracentral difference (OR=1.017, 95% CI=1.002 to 1.033, and *P=0.023*), and central difference (OR=1.026, 95% CI=1.007 to 1.045, and *P=0.007*). In the multivariate logistic regression, NTG eyes were significantly associated with CCT (OR=0.990, 95% CI=0.986 to 0.994, and *P<0.001*), diastolic blood pressure (OR=0.981, 95% CI=0.969 to 0.993, and *P=0.002*), female (OR=1.827, 95% CI=1.433 to 2.330, and *P=0.005*), age (OR=1.021, 95% CI=1.013 to 1.028, and *P<0.001*), and central difference (OR=1.022, 95% CI=1.002 to 1.042, and *P=0.028*).

Discussion:

This study was based on a large-scale Chinese cohort containing POAG and OHT patients without previous treatment. The outcomes of our cross-sectional comparative study revealed there were distinct differences in terms of clinical characteristics and patterns of visual field defect between NTG and HTG. While both NTG and HTG had worse VF defects in the superior hemifield, NTG had greater hemifield asymmetricity than HTG, after stratification by disease severity. Thinner CCT, older age, a larger proportion of female, lower diastolic blood pressure, and greater central regional asymmetry of VF are clinical factors associated with NTG in the multivariate logistic regression.

The baseline clinical characteristics were different in HTG and NTG. While the HTG patients tended to be younger and more myopic, the NTG patients were older[31], with higher female/male ratio[1,33], and had thinner CCT[31,32]. This observation was consistent with previous studies[1,31-33]. Importantly, as thinner CCT is believed to affect the measurement of IOP[34], it is possible that some patients in the NTG group (higher teen) have a similar etiology as HTG[32]. Myopia is a risk factor for open-angle glaucoma[35,36]. And Lin F. et. found that nearly 10.8% highly myopic eyes showed glaucoma-like defects.[45] The VF damage associated with high myopia in HTG may be worse than NTG.

Moreover, the prevalence of hypertension and ischemic heart disease in NTG group was

higher than HTG group($P<0.05$ for both comparisons). This result is consistent with the hypothesis that vascular dysfunction is a risk factor for NTG[12]. However, we should also mention that the mean age of NTG was older than HTG in our cohort, which might affect difference of disease prevalence. Although some investigators found that migraine was a risk factor for NTG progression[37], only three HTG patients, and no NTG, reported migraine in our cohort.

Among all eyes who initiated hypotensive treatment in our cohort, 30.6% HTG but only 19.7% NTG were at the pre-perimetric stage. This rate was much higher than that in EMGTS[38], in which only 9 in 316 eyes were defined as normal or borderline, but comparable to CIGTS (21% within normal limits and 9% scored borderline)[39]. The different proportions between NTG and HTG might be attributed to the difference in the clinical manifestation and diagnosis criteria of HTG and NTG. For HTG, both IOP elevation and optic-disc excavation could provide some hints, while in NTG, most patients remained unaware of their disease until visual disturbance appeared. In a recent study of visual field progression in glaucoma subtypes[40], they found that the progression of pre-perimetric OAG was relatively lower than established OAG with established visual field defects. However, in a Long-Term Follow-up in Pre-perimetric Open-Angle Glaucoma study[41], there was no significant difference in baseline IOP between progressors and non-progressors. The relative high rate of pre-perimetric OAG and the imbalance of its distribution in HTG and NTG might affect disease progression in future analyses.

The global indices, severity of disease in patients with VFD, and trend across stages were similar between HTG and NTG. The overall matched parameters strongly implies that it is appropriate to combined the two subgroups in subsequent analysis. While LiGHT-China was based on the protocol as Light-UK, the proportion eyes with severe stage VFD (10.6%, 117 severe OAG eyes/1105 OAG eyes)[26] was relatively higher than the LiGHT-UK (8.8%, 75 severe OAG eyes/855 OAG eyes)[44]. However, this scenario was more profound in this study when the stages were categorized by more stringent creteria (18.7%, 207 severe OAG eyes/1105 OAG eyes), in addition to providing information on global loss based on MD and visual field defects close to the fixation point that can severely threaten patient vision are also considered[42]. Some studies for the progression of NTG found that the central VF progression was related to autonomic dysfunction[11] and vascular etiology[12]. And in a 5-year follow-up study on normal-tension glaucoma (NTG), they found that NTG patients with central VF defects at baseline are at increased risk of progression compared with those with peripheral VF defect[43]. Thus, a relatively large proportion of NTG and a large scale of patients with central VF defects at baseline in LiGHT-China might affect the future progression characteristics.

Although there have been reports regarding on the difference of visual defect patterns between NTG and HTG, our study was the first to demonstrate it in a large-scale treatment-naïve cohort in Chinese population. Similar to other studies conducted in Korean and Chinese[16-18], we observed more severe visual field defect in the superior central region in NTG population. Moreover, the NTG patients in LiGHT-China tend to have higher rate of hypertension and ischemic heart disease. These findings supported the hypothesis of pressure-independent mechanism in the pathogenesis of NTG, perhaps macular retinal ganglion cells have higher oxygen demands, thus more vulnerable to ischemic damage[12].

Based on this theory, the response to treatment of the two subgroups might be different, which will be addressed in the follow-up study.

Our study has several limitations. First, according to the role of recruitment criteria of Light-China, eligible eyes but not patients were analyzed, thus the bilaterality might have confound the association between possible risk-factors. However, the number of subjects were relatively balanced between groups. Second, this study was not based on a population-based cohort, thus there was selection bias in term of the of natural presentation of two-subgroups. Widespread reliance of IOP for case detection as is seen in the UK led to one study finding that all undiagnosed POAG patients had normal IOP. (REF to EPIC Norfolk paper) This is because high IOP might lead to a cases being detected earlier with more mild VF loss, whereas more central or more severe VF loss arise before self-referral in normal pressure eyes.

In conclusion, this study showed that NTG and HTG had similar disease severity at enrollment. The two subtypes both showed worse superior defects but NTG had greater hemifield asymmetricity, supporting the hypothesis that the pathogenesis of NTG and HTG may arise from different contributions of factors such as vascular inefficiency.

Reference

1. Kim CS, Seong GJ, Lee NH, Song KC, Namil Study Group KGS: Prevalence of primary open-angle glaucoma in central South Korea the Namil study. *Ophthalmology* 2011, 118(6):1024-1030.

2. Liang YB, Friedman DS, Zhou Q, Yang X, Sun LP, Guo LX, Tao QS, Chang DS, Wang NL, Handan Eye Study G: Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. *Invest Ophthalmol Vis Sci* 2011, 52(11):8250-8257.

3. Iwase A, Suzuki Y, Araie M, Yamamoto T, Abe H, Shirato S, Kuwayama Y, Mishima HK, Shimizu H, Tomita G *et al*: The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. *Ophthalmology* 2004, 111(9):1641-1648.1.

4. Shen SY, Wong TY, Foster PJ, Loo JL, Rosman M, Loon SC, Wong WL, Saw SM, Aung T: The prevalence and types of glaucoma in malay people: the Singapore Malay eye study. *Invest Ophthalmol Vis Sci* 2008, 49(9):3846-3851.

5. Araie M: Pattern of visual field defects in normal-tension and high-tension glaucoma. *Curr Opin Ophthalmol* 1995, 6(2):36-45.

6. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998;126(4):487-497.

7. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120(10):1268-1279.

8. Yamamoto T, Kitazawa Y. Vascular pathogenesis of normal-tension glaucoma: a possible pathogenetic factor, other than intraocular pressure, of glaucomatous optic neuropathy. *Prog Retin Eye Res*. 1998;17(1):127-143.

9. Park JH, Jun RM, Choi KR. Significance of corneal biomechanical properties in patients with progressive normal-tension glaucoma. *Br J Ophthalmol*. 2015;99(6):746-751.

10. Iwata, K., Fukuchi, T., Kurosawa, A. (1991). The Histopathology of the Optic Nerve in Low-Tension Glaucoma. In Glaucoma Update IV. Edited by Krieglstein, G.K. Berlin:Springer-

Verlag.1991:120-124.
11. Park HY, Park SH, Park CK. Central visual field progression in normal-tension glaucoma patients with autonomic dysfunction. *Invest Ophthalmol Vis Sci*. 2014;55(4):2557-2563.
12. Choi J, Kook MS. Systemic and Ocular Hemodynamic Risk Factors in Glaucoma. *Biomed Res Int*. 2015;2015:141905.
13. Caprioli J, Spaeth GL. Comparison of visual field defects in the low-tension glaucomas with those in the high-tension glaucomas. Am J Ophthalmol. 1984;97(6):730-737.
14. Thonginnetra O, Greenstein VC, Chu D, Liebmann JM, Ritch R, Hood DC. Normal versus high tension glaucoma: a comparison of functional and structural defects. J Glaucoma. 2010;19(3):151-157.
15. Araie M, Yamagami J, Suziki Y. Visual field defects in normal-tension and high-tension glaucoma. Ophthalmology. 1993;100(12):1808-1814.
16. Park IK, Kim KW, Moon NJ, Shin JH, Chun YS. Comparison of Superior and Inferior Visual Field Asymmetry Between Normal-tension and High-tension Glaucoma. J Glaucoma. 2021;30(8):648-655.
17. Park JH, Yoo C, Park J, Kim YY. Visual Field Defects in Young Patients With Open-angle Glaucoma: Comparison Between High-tension and Normal-tension Glaucoma. J Glaucoma. 2017;26(6):541-547.
18. Jiang J, Ye C, Zhang C, et al. Intraocular asymmetry of visual field defects in primary angle-closure glaucoma, high-tension glaucoma, and normal-tension glaucoma in a Chinese population. Sci Rep. 2021;11(1):11674.
19. Iester M, De Feo F, Douglas GR. Visual field loss morphology in high- and normal-tension glaucoma. J Ophthalmol. 2012;2012:327326.
20. Motolko M, Drance SM, Douglas GR. Visual field defects in low-tension glaucoma. Comparison of defects in low-tension glaucoma and chronic open angle glaucoma. Arch Ophthalmol. 1982;100(7):1074-1077.
21. Heijl A, Bengtsson B, Hyman L, Leske MC; Early Manifest Glaucoma Trial Group. Natural history of open-angle glaucoma. Ophthalmology. 2009;116(12):2271-2276.
22. Lascaratos G, Garway-Heath DF, Burton R, et al. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, double-masked, placebo-controlled trial: baseline characteristics. Ophthalmology. 2013;120(12):2540-2545.
23. Cartwright MJ, Anderson DR. Correlation of asymmetric damage with asymmetric intraocular pressure in normal-tension glaucoma (low-tension glaucoma). Arch Ophthalmol. 1988;106(7):898-900.
24. Crichton A, Drance SM, Douglas GR, Schulzer M. Unequal intraocular pressure and its relation to asymmetric visual field defects in low-tension glaucoma. Ophthalmology. 1989;96(9):1312-1314.
25. Haefliger IO, Hitchings RA. Relationship between asymmetry of visual field defects and intraocular pressure difference in an untreated normal (low) tension glaucoma population. Acta Ophthalmol (Copenh). 1990;68(5):564-567.
26. Yang Y, Jiang Y, Huang S, et al. Laser in Glaucoma and Ocular Hypertension Trial (LIGHT) in China - A Randomized Controlled Trial: Design and Baseline Characteristics. Am J Ophthalmol. 2021;230:143-150.
27. Yang Y, Zhang X, Chen Z, et al. Intraocular pressure and diurnal fluctuation of open-angle

glaucoma and ocular hypertension: a baseline report from the LiGHT China trial cohort . Br J Ophthalmol. 2022;bjophthalmol-2021-320128.
28. Konstantakopoulou E, Gazzard G, Vickerstaff V, et al. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics. Br J Ophthalmol. 2018;102(5):599-603.
29. Anderson DR, Hodapp E. Clinical Decisions in Glaucoma. St Louis, MO: The CV Mosby Co.; 1993.
30. Asman P, Heijl A. Glaucoma Hemifield Test. Automated visual field evaluation. Arch Ophthalmol. 1992;110(6):812-819.
31. Wang D, Huang W, Li Y, et al. Intraocular pressure, central corneal thickness, and glaucoma in chinese adults: the liwan eye study. Am J Ophthalmol. 2011;152(3):454-462.e1.
32. Copt RP, Thomas R, Mermoud A. Corneal thickness in ocular hypertension, primary open-angle glaucoma, and normal tension glaucoma. Arch Ophthalmol. 1999;117(1):14-16.
33. Iwase A, Suzuki Y, Araie M, et al. The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology. 2004;111(9):1641-1648.
34. Manni G, Oddone F, Parisi V, Tosto A, Centofanti M. Intraocular pressure and central corneal thickness. Prog Brain Res. 2008;173:25-30.
35. Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology. 2011;118(10):1989-1994.e2.
36. Chon B, Qiu M, Lin SC. Myopia and glaucoma in the South Korean population. Invest Ophthalmol Vis Sci. 2013;54(10):6570-6577.
37. Drance S, Anderson DR, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001;131(6):699-708.
38. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology. 1999;106(11):2144-2153.
39. Gillespie BW, Musch DC, Guire KE, et al. The collaborative initial glaucoma treatment study: baseline visual field and test-retest variability. Invest Ophthalmol Vis Sci. 2003;44(6):2613-2620.
40. De Moraes CG, Liebmann JM, Liebmann CA, Susanna R Jr, Tello C, Ritch R. Visual field progression outcomes in glaucoma subtypes. Acta Ophthalmol. 2013;91(3):288-293.
41. Kim KE, Jeoung JW, Kim DM, Ahn SJ, Park KH, Kim SH. Long-term follow-up in preperimetric open-angle glaucoma: progression rates and associated factors. Am J Ophthalmol. 2015;159(1):160-8.e82.
42. Brusini P, Johnson CA. Staging functional damage in glaucoma: review of different classification methods. Surv Ophthalmol. 2007;52(2):156-179.
43. Raman P, Suliman NB, Zahari M, Mohamad NF, Kook MS, Ramli N. Baseline Central Visual Field Defect as a Risk Factor For NTG Progression: A 5-Year Prospective Study. J Glaucoma. 2019;28(11):952-957.
44. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial . Lancet. 2019;393(10180):1505-1516.
45. Lin F, Chen S, Song Y, et al. Classification of Visual Field Abnormalities in Highly Myopic

438 Eyes without Pathologic Change. Ophthalmology. 2022;129(7):803-812.