RETROSPECTIVE COHORT STUDY

Decision Factors for Glaucoma Suspects and Ocular Hypertensive Treatment at an Academic Center

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Abstract

Aims and background: Practice guidelines assert that high-risk glaucoma suspects should be treated. Yet, there is ambiguity regarding what constitutes a high enough risk for treatment. The purpose of this study was to determine which factors contribute to the decision to treat glaucoma suspects and ocular hypertensive patients in an academic ophthalmology practice.

Materials and methods: Retrospective cohort study of glaucoma suspects or ocular hypertensives at an academic ophthalmology practice from 2014 to 2020. Demographics, comorbidities, intraocular pressure (IOP), optical coherence tomography (OCT) findings, and visual field measurements were compared between treated and untreated patients. A multivariable logistic regression model assessed predictors of glaucoma suspected treatment.

Results: Of the 388 patients included, 311 (80%) were untreated, and 77 (20%) were treated. There was no statistical difference in age, race/ethnicity, family history of glaucoma, central corneal thickness (CCT), or any visual field parameters between the two groups. Treated glaucoma suspects had higher IOP, thinner retinal nerve fiber layers (RNFL), more RNFL asymmetry, thinner ganglion cell–inner plexiform layers (GCIPL), and a higher prevalence of optic disc drusen, disc hemorrhage, ocular trauma, and proliferative diabetic retinopathy (PDR) ($p < 0.05$ for all). In the multivariable model, elevated IOP {odds ratio [OR] 1.16 [95% confidence interval (CI) 1.04–1.30], $p = 0.008$}, yellow temporal [5.76 (1.80–18.40), $p = 0.003$] and superior [3.18 (1.01–10.0), $p = 0.05$] RNFL quadrants, and a history of optic disc drusen [8.77 (1.96–39.34), $p = 0.005$] were significant predictors of glaucoma suspect treatment.

Conclusion: Higher IOP, RNFL thinning, and optic disc drusen were the strongest factors in the decision to treat a glaucoma suspect or ocular hypertensive patient. RNFL asymmetry, GCIPL thinning, and ocular comorbidities may also factor into treatment decisions.

Clinical significance: Understanding the clinical characteristics that prompt glaucoma suspect treatment helps further define glaucoma suspect disease status and inform when treatment should be initiated.

Keywords: Cohort study, Ganglion cell–inner plexiform layer, Glaucoma suspect, Retinal nerve fiber layer, Treatment, Visual field.

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Introduction

Glaucoma is one of the leading causes of blindness worldwide, and 76 million individuals between 40 and 80 years of age are estimated to suffer from the disease currently.[1] A glaucoma suspect is an individual who possesses clinical findings or risk factors that indicate increased likelihood of developing glaucoma, which may include elevated intraocular pressure (IOP), suspicious-appearing optic nerve heads (ONH), and/or abnormal visual fields.[2–4] The Ocular Hypertension Treatment Study (OHTS) found that nontreated ocular hypertensives are at an increased risk of developing glaucoma compared to treated patients. Most patients in this study did not go on to develop glaucoma over 5 years; however, by 20 years, the cumulative incidence of developing primary open-angle glaucoma (POAG) was 42% among treated participants and 49% among observed participants.[5,6]

Although glaucoma suspects often develop glaucoma, there is a lack of uniformity regarding when to initiate treatment in these patients.[2,7] The OHTS and additional studies found a variety of risk factors for the development of POAG that should be considered when determining how to manage glaucoma suspect patients, including older age, African American race, Hispanic ethnicity, male sex, larger cup-to-disc ratios (CDR), high IOP, family history of glaucoma, higher visual field standard deviation, greater pattern standard deviation (PSD), type 2 diabetes, high myopia, and a thinner central corneal measurement.[4,5,8–12] The American Academy of Ophthalmology's Preferred Practice Pattern on management of glaucoma suspect patients recommends determining if a patient is at high risk for developing glaucomatous optic neuropathy while considering the potential benefits and risks of treatment.[4] However,

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Conflict of interest: None

there is ambiguity regarding what constitutes high enough risk for treatment. We suspect that there may be distinguishable characteristics between treated and untreated glaucoma suspects that vary from the consensus recommendations due to a lack of clarity regarding when glaucoma suspect treatment should be initiated. The purpose of this study is to determine what clinical characteristics played the strongest clinical role in the decision to treat a glaucoma suspect or ocular hypertensive patient.

Materials and Methods

This study was approved by the University of North Carolina's Institutional Review Board. A waiver of informed consent was granted. This study adhered to the Declaration of Helsinki.

Data Source and Study Population

A list of patients 18 years of age and older with International Classifications of Disease 9 and 10 codes of glaucoma suspect (365.0/H40.0), which encompasses ocular hypertension (365.04/H40.05) and borderline glaucoma (365.0/H40.01), seen at Kittner Eye Center from 4th April 2014 to 4th January 2020 was acquired from the Carolina Data Warehouse through the North Carolina Translational and Clinical Sciences Institute. Patients with a diagnosis of glaucoma suspect or ocular hypertension were included regardless of the laterality of the diagnosis. A power calculation with a minimum of power 0.8 was calculated during the planning phase of the study to ensure data was collected on enough patients to determine significant differences in the variables included in the study. Six hundred patients were randomly selected for initial review. In this review, patients with a diagnosis of glaucoma, plateau iris syndrome, anatomic narrow angles, primary/secondary angle closure including angle closure suspect, missing IOP data, as well as patients with a history of laser peripheral iridotomy (LPI) and/or argon laser peripheral iridoplasty (ALPI) were excluded from the study. Specifically, we excluded 212 patients due to a glaucoma diagnosis of angle closure, anatomic narrow angles, plateau iris configuration, or less than three IOP recordings.

Data Extraction

Electronic medical records were reviewed to collect the following variables: glaucoma treatment including medications and selective laser trabeculoplasty (SLT), living status, age, gender, race, ethnicity, family history of glaucoma, systemic and ocular comorbidities, body mass index (BMI), IOP, refraction expressed as spherical equivalent, central corneal thickness (CCT), gonioscopy, CDR, axial length, optical coherence tomography (OCT) macular ganglion cell–inner plexiform layer (GCIPL) thickness, peripapillary retinal nerve fiber layer (RNFL) thickness and ONH measurements obtained with Cirrus high-definition optical coherence tomography (HD-OCT) (Carl Zeiss Meditec, Dublin, California), and visual field testing results from Humphrey Field Analyzer (Zeiss Meditech) 24-2 Swedish interactive thresholding algorithm (SITA) testing (varied between standard and fast). Average GCIPL thickness, average RNFL thickness, 6-sector GCIPL quadrant values, and RNFL quadrant values and colors (white, green, yellow, and red) were collected and recorded as shown in Figure 1. Both quadrant values and colors were assessed due to concerns that providers may emphasize values over colors or vice versa in clinical decision-making. All data, except the history of ocular comorbidities, was obtained from the patient's most recent ophthalmic eye exam. History of ocular comorbidities was collected from all ophthalmic exam notes. Data from eye-specific variables

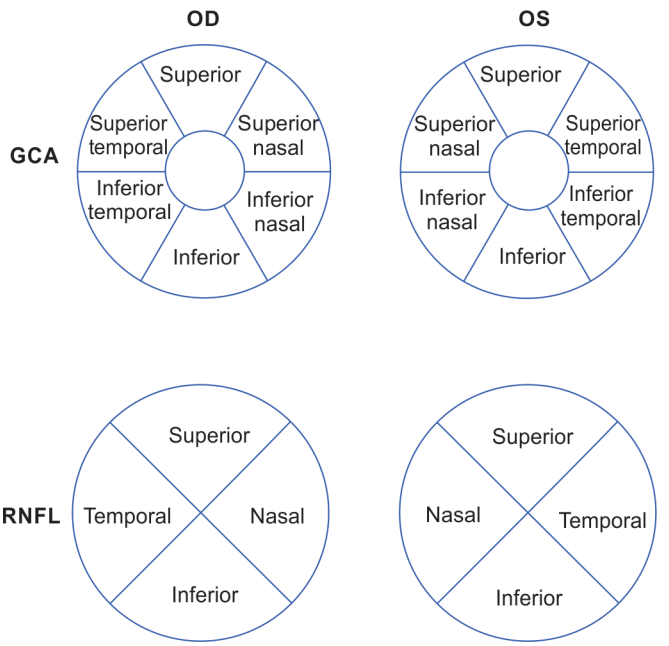

Fig. 1: Ganglion cell analysis and retinal nerve fiber layer secants and quadrants

were collected and recorded from both eyes for each patient [e.g., visual acuity oculus dexter (OD), visual acuity oculus sinister (OS)]. IOP was defined as the average of readings from the three most recent visits to account for physiologic IOP variations, regardless of current treatment or lack thereof. Glaucoma suspect treatment was defined as current treatment with antiglaucomatous medications or history of SLT at the time of data extraction. Visual field parameters included in the analysis were mean deviation (MD), PSD, glaucoma hemifield test (GHT), visual field index (VFI), and reliability indices (fixation loss, false positive rate, and false negative rate).

Data Analysis

Demographics, ocular and systemic comorbidities, IOP, CCT, spherical equivalent, axial length, OCT ONH measurements, RNFL symmetry, average thickness, quadrant colors, quadrant thickness, average GCIPL thickness and quadrants, and visual field measurements were compared with Student's *t*-test for continuous variables and Chi-squared tests for categorical variables between treated versus nontreated glaucoma suspects. Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as frequencies and percentages.

To determine predictors of glaucoma suspect treatment, a multivariable model was used to evaluate the association of demographic variables, comorbidities, baseline ocular, OCT, and visual field parameters with glaucoma suspect treatment. To select variables for the model, we used a Least Absolute Shrinkage and Selection Operator (LASSO) regression. The LASSO regression was done through a cross-validation selection method. This method was chosen because it is well suited to handle a large number of predictor variables that may be correlated. The final multivariable logistic regression model controlled for RNFL symmetry, history of optic disc drusen, left eye IOP, right eye CDR, left temporal RNFL quadrant color and left superior RNFL quadrant color. To account for missingness in the data, the final multivariable logistic model was run only on participants with no missing values in the variables included in the final model. This excluded 35 treated glaucoma

suspects and 85 nontreated suspects. The *p*-values of <0.05 were considered statistically significant. The LASSO regression and multivariable model were performed in R version 4.1.2, and all other statistical analysis was performed in STATA version 15.1 (StataCorp, LP, College Station, Texas).

Results

From the initial review of 600 patients, 388 glaucoma suspect and ocular hypertensive patients were included in the analysis. Of the 388 included, 77 (19.8%) were treated, and 311 (80.2%) were untreated. The average age of the cohort was 65.3 years, and 56% were female. Over half of the patients identified as White/Caucasian as their primary race, whereas nearly 30% identified as Black/African American and 3% as Asian (Table 1). Hispanic/Latino ethnicity accounted for 8.5% of patients. There was no statistical difference in demographic characteristics or family history of glaucoma between untreated and treated patients.

Overall, treated glaucoma suspects had more ocular comorbidities than nontreated suspects [mean 1.17 (standard deviation 0.8) vs 0.95 (0.7) comorbidities, $p = 0.01$, Student's *t*-test]. Treated glaucoma suspects were statistically more likely to have optic disc drusen, disc hemorrhage, ocular trauma, proliferative diabetic retinopathy (PDR), and a history of glaucoma surgery compared to nontreated suspects (Table 1). Overall, ocular comorbidities were uncommon with small sample sizes among both groups. Among the systemic comorbidities assessed, arthritis was significantly more prevalent among nontreated glaucoma suspects compared to treated suspects, but there were no differences between other systemic comorbidities or BMI (Table 1 and Supplementary Table S1).

Average IOP was significantly higher in eyes of treated compared to untreated patients [OD 16.4 (4.3) vs 15.1 (3.1) mm Hg, $p = 0.003$ and OS 16.4 (4.6) vs 15.1 (3.2) mm Hg, $p = 0.002$] (Table 2). There were no statistically significant differences in CCT, spherical equivalent, or axial length between the two groups. Average RNFL was significantly thinner in the treated group [77.2 (22.2) vs 86.5 µm (11.9), $p < 0.001$ OD, and 80.8 (15.6) vs 86.6 (12.3), $p = 0.005$] (Table 3). Further, treated patients had significantly lower RNFL symmetry than untreated patients [66.6% (31.4) vs 78.0% (17.4), $p < 0.001$]. The CDR measured by OCT was smaller in the treated group [0.56 (0.2)] compared to the untreated group [0.63 (0.1), $p = 0.003$] in the left eye only. RNFL quadrant analysis showed that treated glaucoma suspects had significantly thinner nerve fiber layers as measured in microns in all quadrants except for the nasal quadrant of the left eye (Table 3). Similarly, treated patients were significantly less likely to have green RNFL quadrants compared to the untreated groups in all quadrants except the nasal quadrant of the right eye.

In ganglion cell analysis, treated glaucoma suspects had significantly thinner GCIPL in all quadrants of both eyes (Table 4). Additionally, the average and minimum GCIPL was lower among treated glaucoma suspects compared to nontreated suspects [68.5 (13.3) vs 74.2 (11.1), $p = 0.002$ OD and 68.34 (14.3) vs 74.1 (10.2), $p = 0.001$ OS]. Visual field analysis revealed no significant differences between the two groups, including no differences in

Table 1: Patient characteristics and significant comorbidities among nontreated and treated glaucoma suspects

	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Total (N = 388)*
Age (year), mean (SD)	65.9 (14.7)	63.1 (17.0)	0.15	65.3 (15.2)
Gender, *n* (%)				
Female	177 (56.9%)	42 (54.6%)	0.71	219 (56.44%)
Primary race, *n* (%)				
Asian	11 (3.5%)	1 (1.3%)	0.71	12 (3.1%)
Black/African American	91 (29.3%)	24 (31.2%)		115 (29.6%)
White/Caucasian	171 (55.0%)	41 (53.2%)		212 (54.6%)
Other	32 (10.3%)	8 (10.4%)		40 (10.3%)
Unknown	6 (1.9%)	3 (3.9%)		9 (2.3%)
Hispanic/Latino, *n* (%)				
Yes	25 (8.0%)	8 (10.4%)	0.45	33 (8.5%)
No	286 (92.0%)	69 (89.6%)		355 (91.5%)
Family history of glaucoma, *n* (%)				
Yes	75 (24.1%)	21 (27.3%)	0.66	96 (24.7%)
No	118 (37.9%)	25 (32.5%)		143 (36.9%)
Unknown	118 (37.9%)	31 (40.3%)		149 (38.4%)
Number glaucoma medications	0	1.58 (0.82)	NA	NA
Ocular comorbidities, *n* (%)				
Glaucoma surgery	1 (0.32%)	2 (2.63%)	0.04*	3 (0.8%)
Optic disc drusen	5 (1.61%)	5 (6.58%)	0.01*	10 (2.6%)
Disc hemorrhage	2 (0.64%)	3 (3.95%)	0.02*	5 (1.3%)
Trauma	13 (4.18%)	9 (11.84%)	0.01*	22 (5.7%)
PDR	5 (1.61%)	7 (9.21%)	0.001*	12 (3.1%)
Number of ocular comorbidities, mean (SD)	0.95 (0.67)	1.17 (0.82)	0.01*	0.99 (0.70)
Systemic comorbidities, *n* (%)				
Arthritis	105 (33.76%)	16 (20.78%)	0.03*	121 (31.2%)

PDR, proliferative diabetic retinopathy; SD, standard deviation

Table 2: Comparison of IOP, CCT, spherical equivalent, and axial length between nontreated and treated glaucoma suspects

	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Missing N* **(%)**
Average IOP OD				
Mean (SD), mm Hg	15.1 (3.13)	16.4 (4.34)	0.003*	0 (0%)
Average IOP OS				
Mean (SD), mm Hg	15.1 (3.18)	16.4 (4.58)	0.002*	0 (0%)
CCT OD				
Mean (SD), mm Hg	549 (42.4)	560 (56.2)	0.18	183 (47.2%)
CCT OS				
Mean (SD), mm	552 (48.3)	568 (59.4)	0.07	187 (48.2%)
Spherical equivalent OD				
Mean (SD), D	−0.48 (2.63)	−0.72 (2.76)	0.57	114 (29.4%)
Spherical equivalent OS				
Mean (SD), D	−0.71 (2.88)	−0.91 (2.28)	0.64	110 (28.4%)
Axial length OCT				
Mean (SD) OD, mm Hg	24.35 (2.32)	24.42 (1.43)	0.91	291 (75.0%)
Mean (SD) OS, mm Hg	24.38 (2.31)	24.18 (1.33)	0.74	291 (75.0%)

*Statistical significance by *t*-test, $p < 0.05$. CCT, central corneal thickness; IOP, intraocular pressure; OCT, ocular coherence tomography; OD, right eye; OS, left eye; SD, standard deviation

Table 3: OCT, ONH, and RNFL measurements among treated and nontreated glaucoma suspects

	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Missing N (%)*
ONH and average RNFL analysis				
Average RNFL thickness OD, µm	86.51 (11.85)	77.18 (22.22)	<0.001*	106 (27.3%)
Average RNFL thickness OS, µm	86.60 (12.30)	80.80 (15.55)	0.005*	109 (28.1%)
RNFL symmetry, %	78.04 (17.40)	66.60 (31.38)	<0.001*	112 (28.9%)
Rim area OD, mm^2	1.15 (0.22)	1.19 (0.39)	0.37	106 (27.3%)
Rim area OS, mm^2	1.16 (0.23)	1.22 (0.33)	0.10	109 (28.1%)
Disc area OD, mm^2	2.05 (0.46)	2.03 (0.51)	0.78	106 (27.3%)
Disc area OS, mm^2	2.13 (1.30)	1.95 (0.40)	0.33	109 (28.1%)
Difference in disc area, mm^2	0.29 (1.20)	0.41 (0.67)	0.50	103 (26.6%)
Average C-D ratio OD	0.64 (0.11)	0.63 (0.14)	0.59	108 (27.6%)
Average C-D ratio OS	0.63 (0.13)	0.58 (0.15)	0.02*	113 (29.1%)
Difference in average C-D ratio	0.06 (0.09)	0.14 (0.20)	<0.001*	102 (26.3%)
Vertical C-D ratio OD	0.64 (0.43)	0.59 (0.17)	0.43	106 (27.3%)
Vertical C-D ratio OS	0.61 (0.12)	0.56 (0.18)	0.02*	109 (28.1%)
Difference in vertical C-D ratio	0.10 (0.42)	0.13 (0.18)	0.54	103 (26.6%)
Cup volume OD, mm^3	0.34 (0.22)	0.31 (0.26)	0.37	106 (27.3%)
Cup volume OS, mm^3	0.33 (0.22)	0.26 (0.24)	0.047*	109 (28.1%)
Artifacts OD, *n* (%)	22 (9.48%)	1 (2.00%)	0.08	106 (27.3%)
Artifacts OS, *n* (%)	19 (8.26%)	2 (4.08%)	0.31	109 (28.1%)
RNFL quadrant analysis				
Temporal thickness OD, µm	61.83 (12.18)	57.16 (20.74)	0.03*	106 (27.3%)
Temporal color OD				
White	13 (5.58%)	7 (13.46%)	0.005*	107 (27.6%)
Green	200 (85.84%)	33 (63.46%)		
Yellow	10 (4.29%)	5 (9.62%)		
Red	8 (3.43%)	5 (9.62%)		

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	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Missing N (%)*
Superior thickness OD, µm	102.24 (17.89)	91.76 (29.40)	0.001*	106 (27.3%)
Superior color OD				
White	4 (1.72%)	2 (3.85%)	0.001*	107 (27.6%)
Green	183 (78.54%)	27 (51.92%)		
Yellow	25 (10.73%)	8 (15.38%)		
Red	19 (8.15%)	13 (25.0%)		
Nasal thickness OD, µm	70.86 (12.95)	64.50 (18.73)	0.004*	106 (27.3%)
Nasal color OD				
White	16 (6.87%)	4 (7.69%)	0.10	107 (27.6%)
Green	209 (89.70%)	43 (82.69%)		
Yellow	6 (2.58%)	2 (3.85%)		
Red	0 (0%)	1 (1.92%)		
Inferior thickness OD, µm	110.90 (19.68)	95.20 (34.87)	<0.001*	106 (27.3%)
Inferior color OD				
White	17 (7.30%)	4 (7.69%)	0.001*	107 (27.6%)
Green	182 (78.11%)	33 (63.46%)		
Yellow	22 (9.44%)	3 (5.77%)		
Red	10 (4.29%)	10 (19.23%)		
Temporal thickness OS, µm	61.56 (13.24)	56.35 (12.87)	0.01*	109 (28.1%)
Temporal color OS				
White	15 (6.44%)	1 (1.96%)	0.001*	110 (28.4%)
Green	196 (84.12%)	35 (68.63%)		
Yellow	9 (3.86%)	9 (17.65%)		
Red	9 (3.86%)	4 (7.84%)		
Superior thickness OS, µm	106.46 (17.09)	97.55 (24.04)	0.002*	109 (28.1%)
Superior color OS				
White	6 (2.58%)	1 (1.96%)	0.001*	110 (28.4%)
Green	189 (81.12%)	28 (54.90%)		
Yellow	12 (5.15%)	8 (15.69%)		
Red	22 (9.44%)	12 (23.53%)		
Nasal thickness OS, µm	69.37 (11.77)	66.53 (12.92)	0.13	109 (28.1%)
Nasal color OS				
White	13 (5.58%)	4 (7.84%)	0.03*	110 (28.4%)
Green	211 (90.56%)	40 (78.43%)		
Yellow	5 (2.15%)	4 (7.84%)		
Red	0 (0%)	1 (1.96%)		
Inferior thickness OS, µm	110.50 (19.66)	102.35 (24.60)	0.01*	109 (28.1%)
Inferior color OS				
White	11 (4.72%)	1 (1.96%)	0.001*	110 (28.4%)
Green	195 (83.69%)	33 (64.71)		
Yellow	14 (6.01%)	6 (11.76%)		
Red	9 (3.86%)	9 (17.65%)		

*Statistical significance by *t*-test or Chi-squared test, $p < 0.05$. CCT, central corneal thickness; C-D, cup-to-disc; OCT, optical coherence tomography; OD, right eye; ONH, optic nerve head; OS, left eye; RNFL, retinal nerve fiber layer

GHT, VFI, MD, PSD, fixation losses, false positive, or false negative errors (Supplementary Table S2).

In the multivariable analysis, each 1 mm Hg increase in IOP was associated with a 16% increased odds of glaucoma suspect treatment {odds ratio [OR] 1.16 [95% confidence interval (CI), 1.04–1.30], $p = 0.008$} (Table 5). A yellow temporal RNFL quadrant was associated with nearly six times greater odds of glaucoma suspect treatment [OR 5.76 (95% CI, 1.80–18.40), $p = 0.003$], and a yellow superior RNFL quadrant was associated with three times greater odds of treatment [OR 3.18 (95% CI, 1.01–10.0), $p = 0.05$]. Optic disc drusen increased the odds of glaucoma suspect treatment by nearly nine times [OR 8.77 (95% CI, 1.96–39.34), $p = 0.005$]. RNFL symmetry, CDR, and red temporal or superior RNFL quadrants were not significant in the multivariable model.

Discussion

The OHTS elucidated that untreated ocular hypertensive patients are at an increased risk (9.5%) of developing glaucoma compared to those who are treated (4.4%) at 5 years.[5] By 20 years, the risk of developing POAG was much higher, with a slightly larger difference between the two groups (49.3% among nontreated vs 41.9% among treated suspects).[6] Our retrospective study aimed to identify patient characteristics that lead to treatment of glaucoma suspects and ocular hypertension patients in our academic practice.

The IOP is the primary modifiable risk factor in the progression of glaucoma. The goal of treatment for glaucoma suspect, ocular hypertensive, and POAG patients is to lower IOP in order to prevent

Table 4: Optical coherence tomography (OCT) ganglion cell analysis among treated and nontreated glaucoma suspects

	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Missing N (%)*
OCT ganglion cell analysis quadrants, µm				
Superior temporal OD	74.31 (11.60)	69.17 (14.40)	0.008*	112 (28.9%)
Superior OD	74.78 (12.49)	69.46 (16.87)	0.01*	112 (28.9%)
Superior nasal OD	75.51 (11.43)	70.23 (14.43)	0.006*	112 (28.9%)
Inferior nasal OD	74.24 (11.98)	67.54 (14.46)	<0.001*	112 (28.9%)
Inferior OD	72.17 (12.10)	66.17 (14.66)	0.003*	112 (28.9%)
Inferior temporal OD	75.64 (11.24)	69.31 (14.40)	<0.001*	112 (28.9%)
Superior temporal OS	75.16 (10.63)	69.25 (13.72)	0.001*	113 (29.1%)
Superior OS	74.54 (12.51)	68.45 (15.93)	0.004*	115 (29.6%)
Superior nasal OS	74.82 (11.74)	68.70 (16.73)	0.003*	115 (29.6%)
Inferior nasal OS	73.28 (11.74)	67.26 (15.73)	0.003*	115 (29.6%)
Inferior OS	71.65 (12.59)	66.49 (16.61)	0.02*	115 (29.6%)
Inferior temporal OS	75.09 (11.75)	69.98 (14.41)	0.01*	115 (29.6%)
GCLIPL thickness, µm				
Average GCLIPL thickness OD	74.18 (11.14)	68.54 (13.32)	0.002*	112 (28.9%)
Average GCLIPL thickness OS	74.14 (10.21)	68.34 (14.31)	0.001*	115 (29.6%)
Minimum GCLIPL thickness OD	68.53 (15.10)	60.65 (19.75)	0.002*	112 (28.9%)
Minimum GCLIPL thickness OS	67.50 (15.85)	60.89 (19.46)	0.01*	115 (29.6%)

*Statistical significance by *t*-test < 0.05. GCA, ganglion cell analysis; GCIPL, ganglion cell and inner plexiform layer; OD, right eye, OS, left eye

further retinal ganglion cell loss.[4,13] Our study found that IOP was significantly higher in treated patients. Therefore, the measured IOP in our treated patients is lower than their physiologic baseline but still higher than nontreated patients. CCT, another risk factor for POAG,[5,8] is known to affect measurement accuracy of IOP.[14] While our study did not find a significant difference in CCT, there was a trend of higher CCT in the treated glaucoma suspect group. This suggests the possibility that our practitioners were biased toward treating high IOP despite the context of thicker CCT.

Our study also found that providers were more likely to treat when RNFL was thinner or symmetry in RNFL between the eyes lower. The only RNFL quadrant not found to be significantly thinner in the treated group was the nasal quadrant, which is unsurprising as it is less often impacted by glaucomatous damage.[15] Further, treated suspects had significantly thinner average and minimum GCIPL thickness as well as thinner GCIPL quadrants compared to nontreated patients. RNFL thinning, decreased RNFL symmetry, and GCIPL thinning are evidence of glaucomatous damage, and our study suggests these factors were compelling reasons for treatment initiation.[4] Further, both RNFL and GCIPL thinning have been found to have high diagnostic accuracy for glaucoma, and our study demonstrates clinicians' perceived importance of RNFL and GCIPL in glaucoma diagnosis.[16,17] Average and vertical CDR were lower in treated suspects compared to untreated suspects. While we may have expected a higher CDR in treated patients to prompt treatment initiation, findings of a slightly lower CDR may reflect the effectiveness of treatment in preventing cupping and the development of POAG. Additionally, it is possible that there was a greater proportion of patients with physiologic cupping in the untreated group (i.e., patients with large cups but normal RNFL and GCIPL), which could explain this discrepancy.

Treated suspects had a higher total number of ocular comorbidities as well as a higher prevalence of optic disc drusen, disc hemorrhage, and a history of ocular trauma compared to untreated patients. Optic disc drusen, disc hemorrhage, and ocular trauma are nonglaucomatous diseases that may damage the optic disc or cause abnormalities in the appearance of the optic disc or in visual fields.[4,18] These comorbidities may also be associated with changes in parameters that are frequently monitored by glaucoma specialists.[18] Since the result of these disease processes impacts the patients in a manner similar to glaucoma but completely independent of glaucoma, it creates challenges in diagnosis and management. Therefore, treatment in these cases may be occurring as an overabundance of caution, given the difficulty in discerning whether optic nerve changes, RNFL thinning, or visual field abnormalities are occurring due to glaucoma or coexistent comorbidities. Additionally, glaucoma can coexist with anomalous nerves, and our current definitions of glaucoma do not account for these cases.

Although the association of type 2 diabetes mellitus (T2DM) with POAG remains unclear, multiple studies have found that T2DM is an important risk factor for POAG, and the Los Angeles Latino

Table 5: Multivariable model for predictors of glaucoma suspect treatment

	Glaucoma suspect treatment	
	OR (95% CI)	*p-value*
RNFL symmetry	0.99 (0.97–1.01)	0.16
History of optic disc drusen	8.77 (1.96–39.34)	0.005*
IOP OS	1.16 (1.04–1.30)	0.008*
C-D ratio OD	5.93 (0.65–54.15)	0.12
OS temporal RNFL quadrant color		
Yellow	5.76 (1.80–18.40)	0.003*
Red	1.47 (0.30–7.26)	0.63
OS superior RNFL quadrant color		
Yellow	3.18 (1.01–10.0)	0.05*
Red	1.62 (0.53–4.97)	0.40

*Statistical significance by multivariable logistic regression model $p < 0.05$. CI, confidence interval; IOP, intraocular pressure; OD, right eye; OS, left eye; RNFL, retinal nerve fiber layer

Eye Study (LALES) determined that longer duration of T2DM is associated with a higher risk of POAG.[4,19] While our study did not find a significant difference in prevalence of DM or nonproliferative diabetic retinopathy (NPDR) between nontreated and treated patients, PDR was significantly more prevalent among treated glaucoma suspects compared to untreated suspects. This may indicate that while the presence of DM did not directly influence treatment, severe ocular complications of DM pushed providers toward treatment. DM is also known to thin the RNFL.[20] It is possible that RNFL thinning seen in suspects with PDR was thought to be due to glaucoma, resulting in the initiation of glaucoma treatment.

Our study found no difference in age, race/ethnicity, or family history of glaucoma between the two groups. This was unexpected as increased age, African American race, Hispanic/Latino ethnicity, and family history of glaucoma are well-known risk factors for POAG, which we thought might have prompted providers to initiate treatment in glaucoma suspects.[4,21,22] However, our results suggest that these risk factors are not sufficient for providers to initiate treatment in glaucoma suspects. Other findings, such as elevated IOP or suspicious RNFL, were stronger drivers in pushing a provider toward treatment.

Interestingly, there were no significant differences in any visual field parameters between untreated and treated patients. A high PSD is a risk factor associated with POAG.[8,23,24] Visual field deficits, which would lead to lower MD and higher PSD, are an eventual outcome of glaucomatous damage.[8] As outlined in the 2020 POAG Suspect Preferred Practice Pattern, a glaucoma suspect is defined as someone with a visual field suspicious for glaucomatous damage or consistently elevated IOP associated with a normal appearance of the optic disc, normal RNFL, and normal visual field test results.[4] Considering that visual field defects tend to occur later in glaucoma, visual field defects found in isolation may be uncommon.[25] Therefore, patients who are experiencing visual field deficits along with other clinical signs of glaucoma would likely be considered to have POAG and, therefore, would not be included in this study. Additionally, visual fields were highly missing in this study, and only 50% of patients had visual field measurements, which may have minimized differences between the two groups. Further, treated suspects may not have had worse visual field findings if they obtained better disease control with antiglaucoma treatment.

In general, visual field data can be difficult to interpret as there are many factors that may obscure findings. For example, patients with visual field defects due to other disease processes, such as retinal vascular occlusion, may have a visual field defect that looks similar to glaucoma, causing uncertainty regarding the diagnosis.[26] Similarly, patients with myopic optic neuropathy may have an optic disc that appears glaucomatous with associated visual field changes and be incorrectly diagnosed with glaucoma since the absence of progression would be the only distinguishing factor.[27–29] Patients who are incorrectly classified as POAG or glaucoma suspect and included in the analysis can cause ambiguity in research findings.

Thinning in the temporal and superior RNFL quadrants were significant predictors of glaucoma suspect treatment in the multivariable model, with a yellow temporal RNFL quadrant and yellow superior RNFL quadrant increasing odds of treatment by approximately six and three times, respectively. This suggests that RNFL thinning was a strong indication for providers to initiate treatment. Temporal quadrant thinning may be a strong predictor of treatment because many glaucoma suspects have superior and inferior thinning, but thinning of the temporal quadrant suggests more diffuse RNFL thinning, prompting precautionary treatment. Elevated IOP was also a significant predictor of glaucoma suspect treatment in the multivariable model, suggesting that elevated IOP played an important role in the decision to treat. Optic disc drusen were associated with nearly nine times greater odds of glaucoma suspect treatment. We believe this may be because drusen can result in RNFL thinning.[18] Since providers may be unable to determine if the RNFL thinning is a result of the drusen or glaucoma, they may be more likely to treat out of an abundance of caution.

Many patients had missing information, including CDR, optic nerve imaging, and visual field testing. While outside the scope of this investigation, we suspect that some practitioners may find a patient minimally concerning for glaucoma but enough to warrant an examination of the optic nerve. For example, a patient with a positive family history and possibly a thin inferior optic nerve quadrant could be tested with just an OCT to confirm or more accurately represent what was appreciated on clinical examination. If the results were not concerning, a visual field may have been considered superfluous. Future studies looking into what examinations glaucoma suspects are receiving and why are they needed to determine the most effective and efficient studies patients should receive.

This study is subject to multiple limitations. First, this is a single institution study, which can limit the external validity of the study. This was mitigated by the number of patients included in the study and the variety of training experiences of the practitioners at the Kittner Eye Center. Additionally, the Kittner Eye Center serves a broad patient population from across the Research Triangle metropolitan area to rural North Carolina and bordering communities of Virginia, Tennessee, and South Carolina. This represents a diverse patient population and increases the likelihood that these results could be applied to other patient populations. Additionally, visual field measurements and OCT measurements had a high percentage of missing data. Although we accounted for missingness in our models and would assume missingness to be evenly distributed across the two groups, missing data could have biased the results. Further, there are inherent limitations due to the retrospective design and potential for undocumented confounding variables. Fortunately, this design allowed us to examine treatment practices without the potential for observer bias. IOP data were not controlled for use of glaucoma medication. Therefore, the treated IOPs are likely to be underrepresenting the actual pretreatment IOP, which further reinforces the idea that higher IOP was associated with the decision to treat. We included both eyes in the study, considering that glaucoma is typically a bilateral disease. However, we did not obtain information on whether both eyes or only one eye was treated. Interestingly, the left eye average and vertical CDR were significant, while the right eye was not. It is possible that a proportion of patients were treated in the left eye only, which may have contributed to a smaller CDR in the left eye only compared to nontreated participants. Further, we did not document which patients were diagnosed with ocular hypertension versus glaucoma suspect. The decision factors for treatment could vary between these two diagnoses. We did not collect information on which provider was associated with each patient. There may be inter-provider differences in risk factors that may impact the results. Additionally, with there being approximately four glaucoma specialists at our medical center over the period of the study, the small number of providers could limit generalizability of our findings. The number of patients with most ocular comorbidities was small, which limited our ability to make comparisons across groups. It is possible that certain ocular comorbidities may have

been significantly different between the two groups had there been a larger sample size. Further, we did not collect information on when each ocular comorbidity occurred. The timing of the ocular comorbidities may influence the results.

Conclusion

This study serves as an important snapshot of glaucoma suspects and ocular hypertensives in order to disambiguate these diagnoses and highlight factors that influence treatment or lack thereof. In conclusion, our results show that elevated IOP, RNFL thinning and asymmetry, GCIPL thinning, comorbid PDR, optic disc drusen, optic disc hemorrhage, and ocular trauma were associated with the decision to treat glaucoma suspects or ocular hypertensive patients. Elevated IOP, RNFL thinning in the superior and temporal quadrants, and optic disc drusen were the strongest treatment decision factors. Other known glaucoma risk factors, including age, race/ethnicity, family history, CCT, MD, and PSD of visual field testing, were not associated with the decision to treat glaucoma suspects. As this study captures only a point in time, future studies are needed to further delineate the clinical changes that occur over time that prompt glaucoma suspect or ocular hypertensive treatment.

Clinical Significance

This work is one of many needed to better define glaucoma suspect status and progression of glaucoma in order to treat and preserve vision. Understanding the clinical characteristics that prompt glaucoma suspect treatment helps further define glaucoma suspect disease status and inform when treatment should be initiated.

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Table S1: Nonsignificant ocular and systemic comorbidities among nontreated and treated glaucoma suspects

	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Missing N (%)*
Ocular comorbidities, *n* (%)				
Cataract surgery or current cataract	219 (70.42%)	54 (70.13%)	0.96	0 (0%)
BRAO	1 (0.32%)	0 (0%)	0.62	1 (0.3%)
BRVO	5 (1.61%)	0 (0%)	0.27	1 (0.3%)
CRAO	0 (0%)	0 (0%)	NA	1 (0.3%)
CRVO	3 (0.96%)	0 (0%)	0.39	1 (0.3%)
AION	0 (0%)	0 (0%)	NA	1 (0.3%)
Vascular irregularity	7 (2.27%)	2 (2.63%)	0.85	3 (0.8%)
Orbital/cerebral mass	6 (1.93%)	3 (3.95%)	0.30	1 (0.3%)
Unspecified bilateral NPDR	1 (0.32%)	0 (0%)	0.62	0 (0%)
Mild NPDR	14 (4.50%)	2 (2.63%)	0.46	1 (0.3%)
Moderate NPDR	9 (2.89%)	1 (1.32%)	0.44	1 (0.3%)
Severe NPDR	3 (0.96%)	1 (1.32%)	0.79	1 (0.3%)
Peripapillary atrophy	22 (7.07%)	10 (12.99%)	0.13	13 (3.4%)
Systemic comorbidities, *n* (%)				
Asthma	28 (9.00%)	8 (10.39%)	0.71	0 (0%)
Cancer	85 (27.33%)	25 (32.47%)	0.37	0 (0%)
Dementia	6 (1.93%)	1 (1.30%)	0.71	0 (0%)
Depression	69 (22.19%)	10 (12.99%)	0.07	0 (0%)
Diabetes mellitus	110 (35.37%)	26 (33.77%)	0.79	0 (0%)
Hypertension	196 (63.02%)	40 (51.95%)	0.08	0 (0%)
Heart disease	64 (20.58%)	13 (16.88%)	0.47	0 (0%)
Neurodegenerative disease	6 (1.93%)	1 (1.30%)	0.71	0 (0%)
Cerebrovascular disease	36 (11.58%)	10 (12.99%)	0.73	0 (0%)
Number of systemic comorbidities	2.26 (1.59)	1.95 (1.51)	0.12	0 (0%)
BMI	36.47 (115.71)	29.56 (7.80)	0.61	16 (4.1%)

*Statistical significance by *t*-test or Chi-squared test, $p < 0.05$. AION, anterior ischemic optic neuropathy; BRAO, branch retinal artery occlusion; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; NPDR, nonproliferative diabetic retinopathy

Table S2: Visual field measurements among treated and nontreated glaucoma suspects

	Nontreated (N = 311)	*Treated (N = 77)*	*p-value*	*Missing N (%)*
Visual field testing				
GHT OD	1.15 (1.02)	1.13 (1.03)	0.90	189 (48.7%)
GHT OS	1.18 (1.02)	1.44 (1.05)	0.16	191 (49.2%)
VFI OD, %	90.57 (18.01)	88.56 (21.28)	0.55	189 (48.7%)
VFI OS, %	91.63 (15.84)	88.26 (21.63)	0.27	191 (49.2%)
MD OD, dB	−3.74 (6.36)	−4.38 (7.01)	0.58	188 (48.5%)
MD OS, dB	−3.60 (5.68)	−4.81 (6.87)	0.25	190 (49.0%)
PSD OD, dB	3.42 (2.74)	3.00 (1.92)	0.36	188 (48.5%)
PSD OS, dB	3.44 (2.67)	3.32 (2.44)	0.80	190 (49.0%)
Fixation losses OD	0.92 (8.71)	0.19 (0.28)	0.60	189 (48.7%)
Fixation losses OS	0.25 (0.30)	0.20 (0.31)	0.38	192 (49.5%)
False positive errors OD	6.56 (9.83)	4.15 (6.85)	0.15	188 (48.5%)
False negative errors OD	6.31 (8.37)	5.41 (8.23)	0.60	218 (56.2%)
False positive errors OS	6.35 (11.66)	4.95 (6.32)	0.47	188 (48.5%)
False negative errors OS	6.65 (7.68)	6.43 (11.55)	0.90	216 (55.7%)

GHT, glaucoma hemifield test; MD, mean deviation; OD, right eye; OS, left eye; PSD, pattern standard deviation; VFI, visual field index