Article

Evaluation of RETICs Glaucoma Diagnostic Calculators in Preperimetric Glaucoma

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Purpose: To evaluate two glaucoma diagnostic calculators (GDC) in a group of eyes with preperimetric glaucoma (PPG).

Methods: All eyes ($n = 265$) included in this study had ocular hypertension with normal visual fields (VFs) on repeated VF tests. PPG was defined as progression in the Guided Progression Analysis software from Cirrus-optical coherence tomography (GPA-OCT). Three PPG types were defined according to the GPA-OCT software as follows: (1) GPA-OCT with one or more red boxes in two or more columns; (2) GPA-OCT with two or more red boxes in two or more columns; and (3) GPA-OCT with two or more red boxes in two or more columns (definition 2), and in the last scan one or more red box in the RNFL average or quadrants. Nonparametric tests, areas under the receiver operating characteristic curve (AUC), and Bland-Altman tests were assessed.

Results: Definitions one, two, and three were met by 44 (16.6%), 29 (10.9%), and 11 (4.2%) eyes, respectively. The GDC indices (means ± standard deviations) were, respectively, 14.49 ± 21.55% and 26.06 ± 22.50% using the combined and quantitative GDC ($P < 0.001$) in all eyes. Both GDC showed higher glaucoma probability in the PPG group ($P < 0.04$; combined GDC AUCs, 0.720–0.833; quantitative GDC AUCs, 0.700–0.839). GDC values were higher ($P < 0.01$) with greater GPA progression.

Conclusions: The values of both GDC were higher in the PPG group than the ocular hypertension group. The GDC were higher when more columns in the GPA software indicated progression. Both GDC showed a similar ability to detect PPG.

Translational Relevance: These calculators facilitate diagnosis of PPG in ocular hypertensive eyes.

Introduction

Glaucoma, a chronic, progressive disease characterized by loss of the retinal nerve fiber layer (RNFL) and visual field (VF) defects, is diagnosed based on structural and functional tests, such as optical coherence tomography (OCT) and standard automated perimetry (SAP). Early diagnosis of glaucoma is critical to prevent permanent structural damage and irreversible visual loss[1] and is the key to successful treatment and prevention of blindness. Loss of the RNFL precedes VF damage. High-speed, high-resolution imaging of the RNFL has become feasible with introduction of spectral-domain OCT technology for detecting early glaucomatous damage.[2] However, the RNFL thickness evaluated by OCT varies among subjects and is affected by age, disc size, and ethnic background.[3] False-positive cases have been reported depending of the OCT device.[3] Thus, diagnosing glaucoma in the initial stage can be difficult.

Preperimetric glaucoma (PPG) is the earliest stage of open-angle glaucoma defined by RNFL damage without VF defects on SAP.[4,5] The Red Temática de Investigación Corporativa (RETICs) glaucoma diagnostic calculators (GDC) were designed by members

of the Network of Spanish Glaucoma Program (RETICs) to use combinations of different structural parameters to improve the diagnostic ability to detect glaucoma using Cirrus OCT.[6] These GDC analyze and combine the RNFL thickness and optic nerve parameters and other parameters associated with the peripapillary RNFL and macular retinal ganglion cells-inner plexiform layers (GCIPL).[6] The ability to detect glaucoma using these formulas was better than the best parameters of the RNFL, optic disc, and GCIPL analysis used in isolation.[6] These GDC also were validated in another patient sample with good results.[6] We evaluated these GDC in patients with early glaucoma without VF defects to determine if they could be tools for diagnosing PPG.

Methods

Patients with ocular hypertension (OH) were recruited retrospectively in two departments of ophthalmology at the Clínica Universidad de Navarra, Pamplona and the Institut Català de Retina, Barcelona (Spain). The institutional review boards/ethics committees of the institutions approved the study. According to the review committees, no written informed consent was needed for the glaucoma group because data were collected from regular clinical practice. The study adhered to the tenets of the Declaration of Helsinki.

The ophthalmic examinations included slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, dilated stereoscopic fundus examination, gonioscopy, and SAP using the 24-2 Swedish interactive threshold algorithm (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA), and RNFL, optic disc, and GCIPL analysis using Cirrus OCT (Carl Zeiss Meditec). All patients had a spherical equivalent within 5.0 diopters (D) or less, astigmatism of 3.0 D or less, best-corrected visual acuity (VA) of 20/40 or better, no corneal or retinal/macular pathologies, no contraindication to pupillary dilation or intolerance to topical anesthetic or mydriatic agents, and no substantial media opacity. In all examinations the IOP exceeded 20 mm Hg.

VF and OCT Acquisition and Analysis

All patients underwent at least five VF test and five OCT examinations during at least 2 years. All OCT evaluations using Cirrus OCT were performed on the same day as the VF analyses. The Glaucoma Progression Analysis (GPA; Carl Zeiss Meditec,

Dublin, Republic of Ireland) software, a commercially available software that compares an algorithmic method to identify glaucomatous VF progression with the Humphrey Field Analyzer II, was used to evaluate the VFs progression. All patients included in the study had reliable VF tests (fixation losses, false positives, and false negatives all ≤25%). The VF index (VFI) was evaluated in the trend analysis; event analysis also was evaluated to detect progression.

Three OCT volume scans centered on the optic disc were obtained. The RNFL and optic disc measurements were evaluated automatically using the Cirrus OCT system software (version 6.0) on each examination day. After the optic discs were scanned, three new scans were obtained in the macular cube to analyze the GCIPL. The OCT signal strength also was analyzed. Only the best signal strength scan from three obtained scans was selected for RNFL and GCIPL analyses. All OCT scans had a signal strength of 6 or higher. The scans have no misalignments, no empty areas by floaters, or errors in the measurement of the optic disc margins. The Guided Progression Analysis software in the Cirrus OCT (GPA-OCT) was assessed to detect the progression of optic disc and RNFL damage.

If five or more reliable VF tests were obtained and the last VF higher than 95% and without applying the Caprioli's criteria,[7] then the eyes were included. Only VFIs without significant progression in the trend analysis and without event analysis progression were considered normal VF and were included (Fig. 1). All reliable OCT scans were included independently if the RNFL or optic nerve damage progressed in the GPA software.

Preperimetric Glaucoma Definitions

The presence of PPG was defined as eyes with normal VFs and damage progression in the GPA-OCT. In the current study, the following three definitions of PPG according to our GPA-OCT experience regarding progression levels were established: definition one, normal VF and at least one or more red boxes in two or more columns in the GPA-OCT (Fig. 2A); definition two, normal VF and at least two or more red boxes in two or more columns in the GPA-OCT (Fig. 2B); and definition three, normal VF, at least two or more red boxes in two or more columns in the GPA-OCT (definition 2), and in the last scan one or more red cell in the RNFL average or quadrant (Fig. 2C). No other progression criteria of the GPA-OCT summary were included in
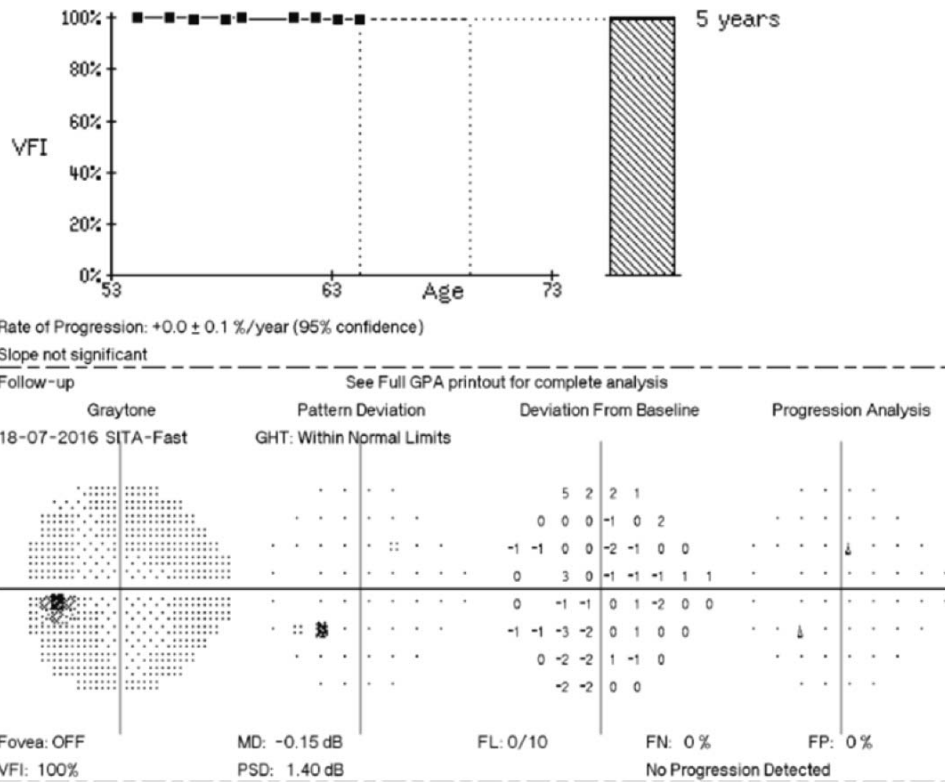
Figure 1. Inclusion criteria of the VF in the Glaucoma Progression Analysis from Humphrey Field Analyzer II. In all VFs, the VFI was higher than 95% and without Caprioli's criteria. The VFI also shows no significant progression in the trend analysis and no event analysis progression.

the PPG diagnoses. To our knowledge, no previous definition of PPG using progression of GPA-OCT has been established.

Glaucoma Diagnosis Calculators

In our previous study of glaucomatous eyes with VF damage, three different predictive models were evaluated using multivariate logistic regression, including one from the numeric data from the RNFL, optic disc, and GCIPLs (quantitative calculator), another using qualitative data in green, yellow, and red (qualitative calculator), and the third using combined qualitative and quantitative data (combined calculator). These GDC were described previously.[6] Briefly, they were designed using a combination of the best predictive parameters to detect perimetric glaucoma, including inferior quadrant RNFL value, inferotemporal GCIPL values, cup/disc ratio average value, cup/disc ratio vertical value, superonasal GCIPL color, superotemporal GCIPL color, minimal GCIPL color, and cup/disc ratio average color (Fig. 3). These GDC indices were analyzed in the study and validation groups, and the

combined and quantitative calculators improved glaucoma detection compared with the best isolated parameters evaluated.[6] The results from the calculator range from 0% (lower probability) to 100% (higher probability). In the current study, both the quantitative and combined calculators were used in the PPG analysis.

Statistical Analysis

The receiver operating characteristic curves (ROCs) were used to determine the discriminatory capabilities between the OH and PPG groups. The best parameters from the RNFL, optic disc, and GCIPL analyses were compared with those from the GDC. Areas under the ROC (AUC) were compared using the Hanley-McNeil method for paired data.[8] Sensitivities of 80% and 95% fixed specificities were calculated. The Kruskal-Wallis and Mann-Whitney nonparametric test were used to compare data. Assuming a range of an AUC value of between 0.7 and 0.85 (10% lower than the values obtained in previous paper where the calculators were developed and validated), with a 5% two-tailed alpha, 80%

Figure 2A:

RNFL and ONH Summary Parameters

		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
Baseline 1:	1	25/04/2013 01:25:47	4000-1386		6/10	103	135	124	1.07	0.70	0.67	0.492
Baseline 2:	2	06/06/2013 09:53:43	4000-1386	R2	7/10	102	136	125	1.05	0.69	0.66	0.455
	3	11/09/2014 11:13:36	4000-1386	R2	7/10	99	131	117	1.03	0.69	0.61	0.454
	4	22/01/2015 10:21:11	4000-1386	R2	9/10	103	129	121	1.03	0.70	0.63	0.460
	5	14/05/2015 10:54:37	4000-1386	R2	9/10	98	131	112	1.00	0.70	0.69	0.490
	6	29/09/2015 10:35:03	5000-4020	R2	7/10	98	128	117	1.11	0.69	0.61	0.452
	7	28/01/2016 11:03:05	5000-4020	R1	6/10	94	126	117	0.99	0.71	0.65	0.509
Current:	8	07/04/2016 10:27:30	5000-4020	R1	8/10	98	128	114	1.01	0.70	0.67	0.465

Figure 2B:

RNFL and ONH Summary Parameters

		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
Baseline 1:	1	25/04/2013 01:25:47	4000-1386		6/10	103	135	124	1.07	0.70	0.67	0.492
Baseline 2:	2	06/06/2013 09:53:43	4000-1386	R2	7/10	102	136	125	1.05	0.69	0.66	0.455
	3	11/09/2014 11:13:36	4000-1386	R2	7/10	99	131	117	1.03	0.69	0.61	0.454
	4	22/01/2015 10:21:11	4000-1386	R2	9/10	103	129	121	1.03	0.70	0.63	0.460
	5	14/05/2015 10:54:37	4000-1386	R2	9/10	98	131	112	1.00	0.70	0.69	0.490
	6	29/09/2015 10:35:03	5000-4020	R2	7/10	98	128	117	1.11	0.69	0.61	0.452
	7	28/01/2016 11:03:05	5000-4020	R1	6/10	94	126	117	0.99	0.71	0.65	0.509
Current:	8	07/04/2016 10:27:30	5000-4020	R1	8/10	98	128	114	1.01	0.70	0.67	0.465

Figure 2C:

RNFL and ONH Summary Parameters

		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
	1	2008 PM	4000-1329		9/10	83	81	117	1.20	0.43	0.51	0.052
	2	2008 AM	4000-1329	R2	8/10	83	83	118	1.30	0.44	0.53	0.054
	3	012 AM	4000-1329	R1	8/10	79	79	111	1.12	0.48	0.59	0.062
	4	013 AM	4000-1386	R2	7/10	77	76	106	1.18	0.49	0.58	0.073
	5	013 5 AM	4000-1386	R2	7/10	78	76	111	1.16	0.52	0.60	0.081
	6	1/20/2014 1:40:20 PM	4000-1386	R2	7/10	77	75	108	1.21	0.49	0.59	0.071
	7	7/1/2014 5:49:21 PM	4000-1386	R2	8/10	77	75	105	1.16	0.49	0.56	0.070
Current:	8	1/13/2015 5:58:14 PM	4000-1386	R2	7/10	73	67	104	1.20	0.51	0.59	0.078

Figure 2. Guided glaucomatous progression from Cirrus OCT with the following three definitions of PPG: one or more *red boxes* in two or more columns (A); two or more *red boxes* in two or more columns (B); and two or more *red boxes* in two or more columns, and in the last scan one or more red quadrant in the RNFL average or in one or more quadrants (C).

power, and assuming that approximately there will be eight noncases for every case (prevalence of preperimetric glaucoma close to 12.5%), then the sample size needed is 261 eyes (29 glaucomatous and 232 nonglaucomatous).

The data were evaluated using SPSS version 20.0.1 software (SPSS, Inc., Chicago, IL), STATA version 12.0 software (Stata Corp, College Station, TX), and MedCalc version 11.2 (MedCalc Software, Mariakerke, Belgium).

Results

Two hundred sixty-five eyes (149 participants) that met the inclusion criteria were enrolled. Table 1 shows the demographic data. Fifty-two (19.6%) eyes underwent five OCT scans, 63 (23.8%) underwent six scans, 47 (17.7%) underwent seven scans, and 103 (38.9%) underwent eight scans.

In the last OCT, the RNFL analyses showed 22 cases

Figure 3A:

GLAUCOMA DIAGNOSTIC CALCULATOR

		TEST RESULT:
Predicted Probability of having Glaucoma	97.0%	**Positive (high probability)**
Age (years)	56	
Superior Nasal Ganglion Cell Color	2	0-Green; 1-Yellow; 2-Red
Superior Temporal Ganglion Cell Color	2	0-Green; 1-Yellow; 2-Red
Minimum Ganglion Cell Color	2	0-Green; 1-Yellow; 2-Red
C/D Ratio Average Color	3	0-Green; 1-Yellow; 2-Red; 3-Grey
Inferior Temporal Ganglion Cell Value	56	
Inferior Retinal Nerve Fiber Layer Value	33	
C/D Ratio Average Value	0.7	
C/D Ratio Vertical Value	0.8	

Figure 3B:

GLAUCOMA DIAGNOSTIC CALCULATOR

		TEST RESULT:
Predicted Probability of having Glaucoma	99.6%	**Positive (high probability)**
Age	56	
Inferior Temporal Ganglion Cell Value	40	
InferiorCF	33	
C/D Ratio Average Value	0.7	
C/D Ratio Vertical Value	0.8	

Figure 3. Excel with both calculators: the combined calculator that uses nine parameters (5 quantitative and 4 qualitative) (A); and the quantitative calculator that uses only five of the quantitative and combined calculator (B).

with red in one quadrant, five cases with red in two quadrants, and one case with red in three quadrants.

Forty-four (16.6%) eyes had PPG that met the first definition, 29 (10.9%) the second definition, and 11 (4.2%) the third definition. The mean ± standard deviation (SD) with the combined GDC was 14.49 ± 21.55% (range, 0.4%–94.7%) and 26.06 ± 22.50% (range, 0.8%–95.9%) with the quantitative GDC in all eyes ($P < 0.001$). Fig. 4 shows the box plots of the values from both GDC in each PPG definition. The

Table 1. Demographic Data

Data	
Number of eyes	265
RE (%)/LE (%)	136 (51.3%)/129 (48.7%)
Number of participants	149
Sex: women (%)/men (%)	90 (60.4%)/59 (39.4%)
Age, yr[a]	64.5 ± 11.1 (25–89)
Number OCT scans[a]	6.8 ± 1.2 (5–8)
Time of follow-up, mo[a]	66.66 ± 16.9 (24–101)
OCT parameters	
Inferior quadrant RNFL value, μ[a]	111.70 ± 15.8 (73–157)
Inferior-temporal ganglion cell value, μ[a]	78.7 ± 7.6 (24–96)
Cup/disc ratio average value[a]	0.56 ± 0.1 (0.07–0.8)
Cup/disc ratio vertical value[a]	0.53 ± (0.06–0.8)
Superior nasal ganglion cell color: yellow (%)/red (%)	8 (3%)/9 (3.4%)
Superior temporal ganglion cell color: yellow (%)/red (%)	10 (3.8%)/19 (7.2%)
Minimum ganglion cell color: yellow (%)/red (%)	21 (7.9%)/14 (5.3%)
Cup/disc ratio average color: yellow (%)/red (%)/gray (%)	23 (8.7%)/16 (6%)/14 (5.3%)

RE, right eye; LE, left eye.
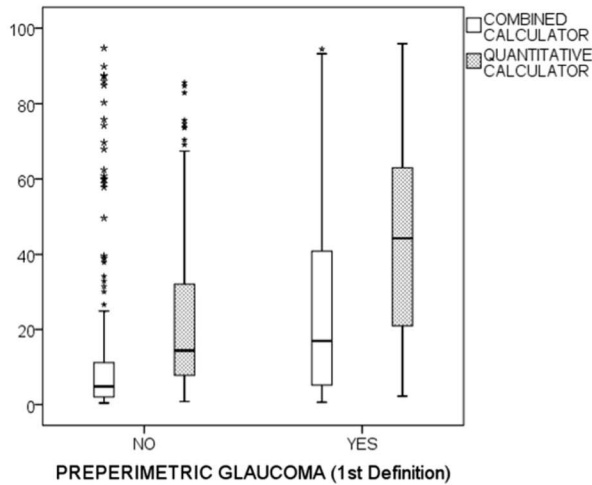[a] Mean and SD (range).

Figure 4A:

PREPERIMETRIC GLAUCOMA (1st Definition)

Figure 4B:

PREPERIMETRIC GLAUCOMA (2nd Definition)
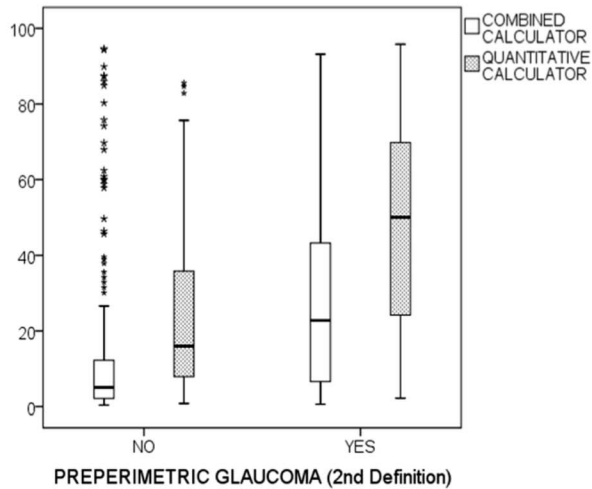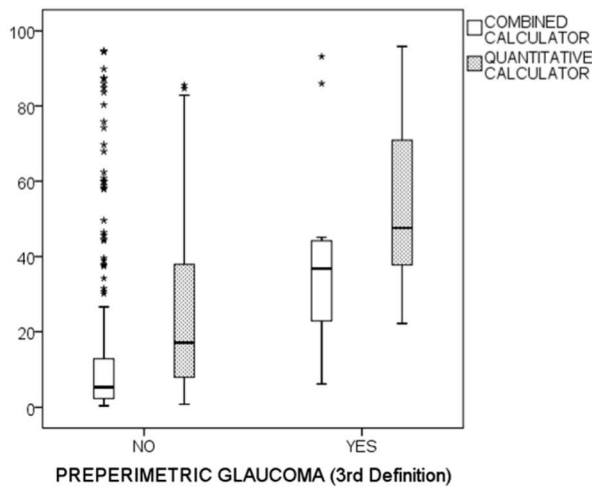
Figure 4C:

PREPERIMETRIC GLAUCOMA (3rd Definition)

combined GDC had more outliers than the quantitative GDC. The OCT trend analysis was evaluated using the three PPG definitions. In the first definition the average RNFL thickness decreased by a mean of -1.51 ± 0.65 µ/year in cases with PPG and 0.37 ± 0.55 µ/year in normal cases ($P < 0.001$). In the second glaucoma definitions these values were 1.64 ± 0.64 µ/year and 0.43 ± 0.66 µ/year in PPG cases and normal cases, respectively ($P < 0.001$). Finally, in the third PPG definition the average RNFL thickness decreased 1.37 ± 0.83 µ/year in PPG and 0.53 ± 0.81 µ/year in normal cases ($P = 0.001$).

Tables 2, 3, and 4 show the AUCs, sensitivity at fixed specificity, and predictive values for the GDC and the best isolated parameters from Cirrus OCT. Regarding the first PPG definition, the quantitative GDC had the better AUC (0.720, 95% confidence interval [CI]: 0.662–0.774) with a positive predictive value of 34.6% compared with the combined GDC (AUC, 0.700; 95% CI, 0.650–0.763). This value was similar to the best isolated parameter (i.e., the inferotemporal ganglion cell value; Table 2). Regarding the second PPG definition, the quantitative GDC also had a higher AUC (AUC, 0.751; 95% CI, 0.695–0.802) than the combined GDC (AUC, 0.729; 95% CI, 0.671–0.781); the best isolated parameter was also the inferotemporal ganglion cell value (AUC, 0.723; 95% CI, 0.665–0.776) (Table 3). Regarding the third PPG definition, the combined GDC had the better AUC (0.839; 95% CI, 0.789–0.881) and the best isolated parameter was the inferior quadrant RNFL value (AUC, 0.838; 95% CI, 0.788–0.880) (Table 4). Figure 5 shows the AUCs for both GDC. We suggested the following cutoff points: 32.9% for the first definition, 46.4% for the second definition, and 29.2% for the third definition for the quantitative GDC. The cutoff values for the combined GDC were 12.2%, 19.5%, and 31.5% for the first, second, and third definitions, respectively.

Finally, the quantitative and combined GDC were compared with the number of columns with two or more red boxes (outside the normal limits). Regarding the quantitative GDC, the means ± SDs were 23.6 ± 20.8 for eyes without red columns (207 eyes), 22.9 ± 19.7 (29 eyes) for eyes with one column with red boxes, 46.1 ± 27.7 (18 eyes) for eyes with two red columns, and 48.3 ± 24.8 (11 eyes) for eyes with three

←

Figure 4. Box plots of the combined and qualitative calculators in all study patients. (A) First glaucoma definition. (B) Second glaucoma definition. (C) Third glaucoma definition.

Table 2. Diagnostic Performance of the Most Relevant Parameters on Evaluated Parameter in the First Preperimetric Glaucoma Definition

Parameter	Area under the ROC (95% CI)	Sensitivity at 80% Specificity	Sensitivity at 95% Specificity	Positive Predictive Value	Negative Predictive Value	LR+	LR−	Best Cutoff
Quantitative Diagnostic Calculator	0.720 (0.662–0.774)	54.6	22.9	34.6	91.3	2.65	0.48	32.9
Combined Diagnostic Calculator	0.700 (0.650–0.763)	52.3	9.1	33.8	90.4	2.56	0.53	12.2
Inferior quadrant RNFL value	0.650 (0.589–0.707)	41.1	18.1	26.3	91.2	1.79	0.49	110
Inferior-temporal ganglion cell value	0.700 (0.641–0.754)	54.5	13.7	31.9	91.8	2.35	0.45	76
Cup/disc ratio average value	0.612 (0.551–0.671)[a]	27.5	3.2	20.6	93.4	1.31	0.35	0.5
Cup/disc ratio vertical value	0.639 (0.578–0.697)	40.9	10.3	21.0	92.9	1.33	0.39	0.5
Superior-nasal ganglion cell color	0.559 (0.497–0.620)[a,b]	15.9	15.9	66.7	85.2	10.1	0.88	Red
Superior-temporal ganglion cell color	0.559 (0.497–0.619)[a,b]	20.5	14.6	31	85.2	2.26	0.87	Yellow
Minimum ganglion cell color	0.559 (0.538–0.659)[a,b]	29.5	17.1	37.1	86.5	2.98	0.78	Yellow
Cup/disc ratio average color	0.543 (0.481–0.604)[a,b]	86.3	86.3	17.9	93.3	1.09	0.36	Red

LR, likelihood ratio.
[a] Statistical difference with the Quantitative Diagnostic Calculator.
[b] Statistical difference with the Combined Diagnostic Calculator.

or four red columns ($P < 0.001$, Kruskal-Wallis test). Regarding the combined GDC, the means ± SDs were 12.8 ± 20.8 for eyes without red columns, 12.2 ± 16.31 for eyes with one column with red boxes, 29.5 ± 30.2 for eyes with two red columns, and 27.6 ± 19.7 for eyes with three or four red columns ($P = 0.001$, Kruskal-Wallis test). The comparison of both GDC with the number of OCT scans was not significant ($P = 0.07$).

Discussion

Calculators are not new in the diagnostic process in medicine; they have been used to detect the risk of bipolar spectrum disorder,[9] kidney disease,[10] prostate cancer,[11] and cardiovascular disease,[12] among others. In 2005, a predictive model was developed to estimate the risk of conversion from OH to glaucoma and validated using the results of the Ocular Hypertension Treatment Study.[13] This risk calculator facilitates an understanding of the 5-year risk of perimetric glaucoma for an individual patient using only five clinical data. Medeiros and Weinreb[14] suggested that using calculators in medicine can help clinicians provide a more objective risk assessment. A calculator might benefit patients regarding costs and cost savings, shorten follow-up, and decrease blindness.[15] These predictive models can provide supplemental information to simplify management of OH and glaucoma and facilitate evidence-based treatment;

Table 3. Diagnostic Performance of the Most Relevant Parameters on Evaluated Parameter in the Second Preperimetric Glaucoma Definition

Parameter	Area Under the ROC (95% CI)	Sensitivity at 80% Specificity	Sensitivity at 95% Specificity	Positive Predictive Value	Negative Predictive Value	LR+	LR−	Best Cutoff
Quantitative Diagnostic Calculator	0.751 (0.695–0.802)	58.6	27.3	37.4	94.4	4.32	0.48	46.4
Combined Diagnostic Calculator	0.729 (0.671–0.781)	58.6	10.3	30.9	94.3	3.64	0.49	19.5
Inferior quadrant RNFL value	0.648 (0.588–0.706)[a]	41.3	13.1	16.7	94.2	1.63	0.50	112
Inferior-temporal ganglion cell value	0.723 (0.665–0.776)	57.6	11.7	26.2	94	2.88	0.52	74
Cup/disc ratio average value	0.664 (0.603–0.720)	37.4	5.4	17.1	93.9	1.68	0.53	0.6
Cup/disc ratio vertical value	0.683 (0.623–0.739)	51.7	16.2	28.9	92.7	3.16	0.61	0.65
Superior-nasal ganglion cell color	0.543 (0.482–0.604)[a,b]	13.8	13.8	44.4	90.2	6.61	0.88	Red
Superior-temporal ganglion cell color	0.537 (0.475–0.598)[a,b]	17.2	10.8	21.1	89.8	2.17	0.92	Red
Minimum ganglion cell color	0.583 (0.521–0.643)[a,b]	27.6	15.2	22.9	90.9	2.41	0.82	Yellow
Cup/disc ratio average color	0.521 (0.459–0.582)[a,b]	82.8	82.8	1.06	0	11.5	93.3	Red

[a] Statistical difference with the Quantitative Diagnostic Calculator.
[b] Statistical difference with the Combined Diagnostic Calculator.

however, their use does not replace the clinician's judgment regarding clinical decision making.[15] We believe that calculators are only one clinical factor that facilitates the complex and difficult diagnosis of PPG.

There is no consensus regarding diagnosis of PPG. Some studies have suggested that these eyes have glaucomatous optic disc abnormalities with localized RNFL damage in the fundus picture but without abnormal VF results.[16] However, this definition is highly subjective and dependent on examiner experience. Thus, Jampel et al.[17] found that the interobserver agreement among glaucoma specialists in judging progressive optic disc changes from stereophotographs was slight to fair. A recent study that evaluated a series of VFs and optic disc photographs of eyes in the Early Manifest Glaucoma Trial with early-to-moderate field loss showed that progression occurred first in the VF more often than in the optic disc.[18] Some authors also have suggested that the diagnostic performance of subjective optic nerve head assessment can be overestimated depending on the optic disc characteristics.[19] We reported previously that the interobserver agreement was higher in images or tests classified as not showing progression than in those classified as having questionable or definitive glaucoma progression.[20] Consequently, it is not easy to evaluate changes or progression by optic disc photography or other subjective methods. The guidelines of the World Glaucoma Association and the European Glaucoma Society advocate regular monitoring of both structural and functional changes,

Table 4. Diagnostic Performance of the Most Relevant Parameters on Evaluated Parameter in the Third Preperimetric Glaucoma Definition

Parameter	Area Under the ROC (95% CI)	Sensitivity at 80% Specificity	Sensitivity at 95% Specificity	Positive Predictive Value	Negative Predictive Value	LR+	LR−	Best Cutoff
Quantitative Diagnostic Calculator	0.833 (0.783–0.876)	72.7	27.3	11.1	99.4	2.89	0.13	29.2
Combined Diagnostic Calculator	0.839 (0.789–0.881)	72.3	26.3	20.5	98.7	5.96	0.31	31.5
Inferior quadrant RNFL value	0.838 (0.788–0.880)	72.7	45.4	13.6	99	3.65	0.23	99
Inferior-temporal ganglion cell value	0.814 (0.762–0.859)	54.5	21.3	10.6	99.4	2.75	0.14	76
Cup/disc ratio average value	0.687 (0.627–0.742)[a,b]	45.4	0	8.3	98.7	2.10	0.30	0.61
Cup/disc ratio vertical value	0.690 (0.630–0.745)[a,b]	36.3	10.7	6.6	100	1.64	0	0.51
Superior-nasal ganglion cell color	0.659 (0.598–0.716)	36.4	35.9	23.5	97.2	7.10	0.67	Yellow
Superior-temporal ganglion cell color	0.679 (0.619–0.734)	45.4	21.6	15.8	96.7	4.33	0.78	Yellow
Minimum ganglion cell color	0.815 (0.763–0.860)	72.7	42.1	22.9	98.7	6.84	0.31	Yellow
Cup/disc ratio average color	0.522 (0.460–0.583)[a,b]	27.7	0	0	95.3	1.13	0	Red

[a] Statistical difference with the Quantitative Diagnostic Calculator.
[b] Statistical difference with the Combined Diagnostic Calculator.

particularly in patients with early glaucomatous damage.[21,22] In the current study, we used the following three different PPG definitions: cases with normal VF, without progression in the VF trend or event analysis, and RNFL loss in the OCT. The first PPG definition is the most initial case of glaucomatous progression; however, it is possible to include false positives. In a previous study of normal eyes,[3] we found a RNFL color-code of yellow or red higher for Cirrus (39%) than for Spectralis (18%) OCT; these results indicated a high proportion of false positives using OCT; however, the use of our GDC obtained normal values in these false positives, which suggested that the GDC can avoid false positives.[23] In the second definition, it is more difficult to have false positives because the definition requires two columns with at least two red boxes in each column. In our experience, these cases progress and indicate that there is glaucomatous damage from PPG. The third definition encompasses the second definition plus red in at least one quadrant of the RNFL. Cutoff values were suggested for every GDC and PPG definition. In order to avoid the false positive that can be included in our PPG definition using the event analysis, we also performed the trend analysis. Thus, the change in the average RNFL thickness is higher in the three PPG definitions than in normal cases. In doubtful cases, if they are glaucomatous cases or a false-positive case, we can obtain the GDC values to facilitate the PPG diagnosis.

The use of these GDC in our previous study of eyes with perimetric glaucoma obtained AUCs of
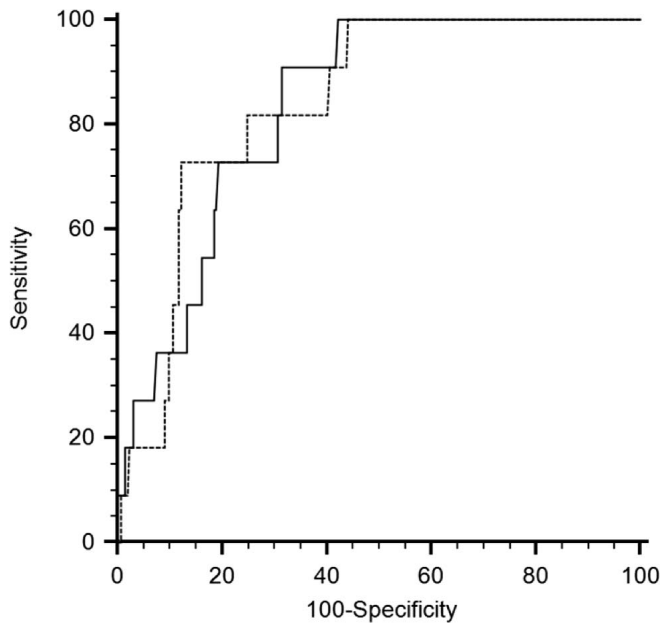
Figure 5. AUCs for the quantitative diagnostic calculator (*solid line*) and the combined diagnostic calculator (*dashed line*) in the third PPG definition.

0.937 (95% CI, 0.911–0.957) for the combined GDC and 0.926 (95% CI, 0.898–0.948) for the quantitative GDC.[6] These results are, as expected, higher than our results with PPG; however, with early perimetric glaucoma the AUCs were 0.909 (95% CI, 0.876–0.936) for the combined GDC and 0.885 (95% CI, 0.849–0.915) for the quantitative GDC when comparing normal cases from the control group with cases in stages 1 and 2 of the Glaucoma Staging System (GSS).[24] With the current PPG definitions, the AUCs varied from 0.720 to 0.833 for the quantitative GDC and 0.700 to 0.839 for the combined calculator. Other previous studies using OCT in PPG obtained similar results. Thus, Pomorska et al.,[25] who compared the Stratus OCT results in 27 eyes with OH, 33 eyes with PPG (defined as the presence of any sign of glaucomatous optic neuropathy in the ophthalmoscopy examination) with 58 normal cases (control group), found AUCs ranging from 0.55 to 0.75 when comparing OH and controls and AUCs ranging from 0.75 to 0.89 when comparing PPG and controls. Hirasawa et al.,[26] using the 3D OCT-2000 (Topcon, Tokyo, Japan), who compared 25 PPG cases with 43 normal cases (control group), obtained the best AUCs for the inferior quadrant RNFL thickness (AUC, 0.907) and for the inferior macular RNFL thickness (AUC, 0.861). However, in the current study, all cases are within grade 0 of the GSS with OH but without VF characteristics of grade I of the GGS, and this

probably justifies the slightly lower values of AUC areas because it is more difficult to identify very early glaucomatous damage. These studies[25,26] also compared normal cases and PPG cases defined as having structural glaucomatous changes seen by ophthalmoscopy, such as rim thinning, notching, and RNFL thinning or defects. Therefore, it is logical to consider that the diagnostic ability of our GDC is lower because they have to detect cases with RNFL loss and those that do not present RNFL loss among cases in group 0 of the GSS and do not use any changes seen on ophthalmoscopy in the optic disc. To facilitate the use of both GDC, we include the website from which to download the Excel (Microsoft, Redmond, WA) files with the values (http://oftared.com/docs/1e633f.xlsx).

This study had limitations. First, the three PPG definitions are related to the structural loss seen on Cirrus OCT, and they can affect the results. However, we compared the eyes with OH with loss of the optic nerve parameters with eyes with OH without changes in these parameters. We think that loss of the optic nerve parameters is crucial for a PPG diagnosis. To reduce the false-positive cases, we included in our definitions only cases with damage in at least two columns, because in our experience, other nonglaucomatous causes can modify one column, especially the RNFL average (e.g., changes in the IOP and RNFL decrease in relation to aging). Moreover, we examined the trend analysis and statistical differences were found between PPG cases and normal cases. We believe that our definitions of PPG include eyes with true optic nerve damage. Second, both eyes of the same patient were analyzed. However, in our previous study of the calculator design,[6] only one eye of a patient was included in both the study group and the validation group. We think that the application of the calculators in both eyes of the same patient does not reduce the quality of our results. Third, our GDC are based on perimetric glaucoma; hence, they should be interpreted with caution in PPG cases. GDC are also constructed in a group of patients evaluated with a certain type of OCT, and should not be extrapolated directly to other OCT devices. However, the good results obtained by our perimetric GDC indicate that they are versatile and consistent calculators because they also obtain very good results in PPG. Despite these limitations, these GDC are easy to use, not time-consuming, and include only nine parameters for the combined GDC and five parameters for the quantitative GDC. We think that these GDC provide new parameters with which to analyze eyes with doubtful

status or artifacts; finally, they can facilitate, in addition to other tests, establishing the PPG diagnosis in clinical practice.

In summary, our GDC indices provided good results and AUCs in eyes with PPG, and in some cases, they were higher than the AUCs of the best isolated OCT parameters. The quantitative GDC used only five parameters, which could be better for scans with all parameters within normal limits (green); the use of the color-code in the combined GDC might improve the PPG diagnosis when any parameters of the final scan are borderline (yellow) or out of the normal limits (red). The quantitative GDC has higher AUCs than the combined GDC, and it might be better in cases with all normal parameters (green). Both GDC facilitate decision making regarding treatment or changing the follow-up in patients with OH. Early detection and treatment of PPG is desirable to avoid progression of the optic disc neuropathy and prevent VF damage.

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