Assessment of Structural Progression in Glaucoma Through Automated Optic Nerve Head Hemoglobin Measurements

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Précis: Automated optic nerve head hemoglobin measurements through change over time in the Globin Individual Pointer (GIP) index, provided by the Laguna ONhE software, can be useful to evaluate structural progression in glaucoma.

Purpose: To assess the performance of automated optic nerve head hemoglobin measurements (ONH Hb) for detection of structural progression in glaucoma patients using event analysis.

Patients and Methods: Treated glaucoma patients were included in this cross-sectional study. Two experienced examiners classified patients into progressors and non-progressors (controls) based on serial color retinographies (CR). Progressors were then subdivided in structural changes of the neuroretinal rim (NR) or retinal nerve fiber layer (RNFL). Globin individual pointer (GIP) index, derived from ONH Hb measurements, was calculated for each CR using the Laguna ONhE software. Differences in GIP values, between baseline and last visit CRs, were used to assess structural progression. Sensitivity at a fixed specificity (50%; median GIP difference in controls) and areas under receiver operating characteristic curves (AUROC) were calculated.

Results: Eight-seven eyes (35 progressors and 52 controls) from 64 patients were enrolled. Mean GIP reduction over time was greater in progressors (-13.0 ± 18.6) than controls (-2.9 ± 10.4; $P = 0.001$). In progressors, mean GIP reduction was greater in patients with NR changes (-19.6 ± 19.5) than RNFL changes (-3.1 ± 12.1; $P = 0.008$). GIP difference correctly identified 69% of the progressors (AUROC: 0.66), being 76% of these progressions related to NR changes (AUROC: 0.76) and 57% to RNFL changes (AUROC: 0.52).

Conclusions: The GIP index, based on automated ONH Hb measurements demonstrated good sensitivity to differentiate progressors from controls, especially in cases in which progression was documented through structural NR changes. Using only 2 CRs and event analysis, GIP changes over time can be a useful screening tool to evaluate structural progression.

Key Words: glaucoma, progression, hemoglobin, optic nerve head, structural damage

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Glaucoma represents an optic neuropathy with structural involvement of the retinal nerve fiber layer (RNFL) and corresponding functional alteration in the visual field (VF) test.[1–3] The disease is responsible for the main cause of irreversible blindness in the world.[4–6] Diagnosis in the early stages, and the detection of disease progression, especially in patients considered rapid progressors, is essential to prevent this unfavorable outcome.[6–9]

Changes over time in VF constitute a way to detect functional progression in glaucoma.[10–12] However, some patients present structural changes that may precede changes in perimetry, especially in the early stages of the disease.[13–15] Qualitative assessment of structural progression can be performed using color retinography or stereophotographs.[16–18] Nonetheless, agreement between examiners, and even among glaucoma specialists, is variable and relatively poor.[19–21] In addition, morphological variations in the optic nerve head and the lack of quantitative assessment can make it difficult to detect progression.[22,23]

The incorporation of optical coherence tomography (OCT) has enabled an objective and quantitative assessment of the structural progression in glaucoma.[24–29] However, the high cost and consequently the difficulty of access in some locations, as well as the lack of interchangeability between different devices, can limit the large use of this tool.[30,31] Therefore, detecting progression can represent a challenging situation in clinical practice.[32,33]

On the basis of the theory of vascular damage in the pathophysiology of glaucoma,[34–36] previous studies have demonstrated low levels of optic nerve head hemoglobin measurements (ONH Hb) in patients with the disease.[37,38] The estimation of ONH Hb is carried out by colorimetric analysis of color retinography (CR) using the Laguna ONhE software, an easy-to-use, fast, noninvasive and low-cost device.[37–39] A previous study from our group and other studies have already demonstrated the good reproducibility and adequate diagnostic performance of the Glaucoma

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Discriminant Function index (GDF) calculated by the software.[40,41] Recently, a newer index (Globin Individual Pointer-GIP), which seems to present greater stability than GDF over time, is being analyzed to detect progression, in assessment with longitudinal analysis.[42,43] However, trend analysis requires a greater number of examinations and can be significantly influenced by outliers, presenting poor performance in detecting sporadic progression. In this context, the purpose of this study was to analyze the performance of automated estimation ONH Hb through the GIP index as a first-stage assessment of structural progression in glaucoma based on an event analysis.

MATERIALS AND METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board/ethics committee of the Federal University of São Paulo (3.937.978). All participants were instructed and signed a written informed consent.

Participants

Patients with treated primary open angle glaucoma and a minimum follow-up of 2 years were enrolled in this observational cross-sectional study. The definition of glaucomatous optic neuropathy was the same as that used in a study by our research group.[41] This was based on the presence of vertical-cup-to-disc-ratio (VCDR) ≥ 0.6, VCDR asymmetry > 0.2 between the eyes, detection of localized or diffuse neuroretinal rim (NR) or RNFL defects, not justified by other pathologies.[41] Inclusion criteria consisted of best-corrected visual acuity $\geq 20/30$ and at least 2 previous CRs and 3 reliable VF examinations. Exclusion criteria consisted of age under 18 years, myopia > -5.00 diopters, previous ocular trauma, intraocular surgery < 6 months before inclusion (except uneventful cataract surgery), diagnosis of primary angle closure or secondary glaucoma, and any ocular alteration that could interfere with CR or VF evaluation (such as diabetic or hypertensive retinopathy, age-related macular disease, or macular edema).

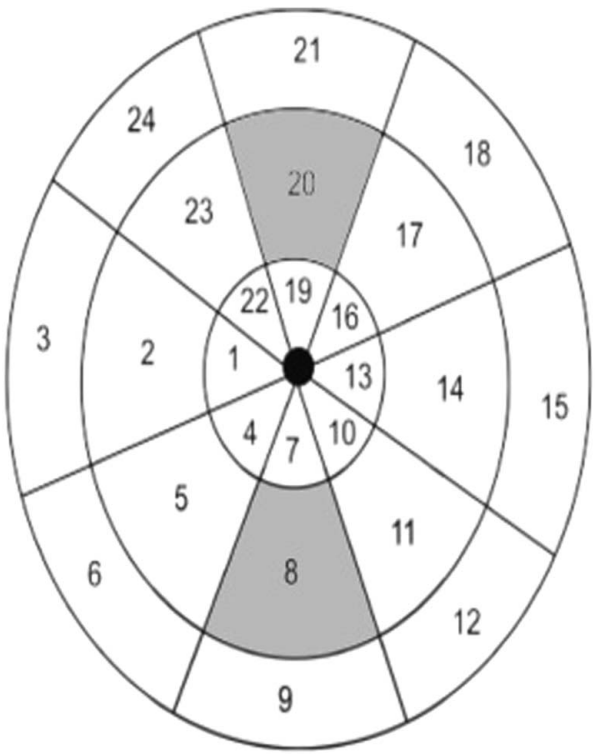

FIGURE 1. Division of the optic nerve head into 24 parts to estimate hemoglobin levels by sector. Sectors 8 and 20, in the vertical region, are highlighted.

Examinations and Data Collection

All patients were submitted to a complete ophthalmological examination including clinical history, best-corrected visual acuity, anterior biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, and fundoscopy evaluation. The following examinations were also performed: CR (Visucam Lite, Carl Zeiss Meditec) and VF test-SITA standard 24-2 (Humphrey Systems). VF reliability criteria were: fixation loss $< 20\%$ and false negatives and positives $< 33\%$. Only reliable VF were included in the present study.

After inclusion, serial color retinographies and disc photos of the participants were reviewed by 2 experienced glaucoma examiners (T.S.P. and S.H.T.) for the presence of definitive anatomical progression. Eyes were then divided into 2 groups: progressors and controls (eyes with stable disease). Progressors were then classified depending on how the progression was documented through CR: based on structural changes of the NR (progressive localized or global NR loss) or RNFL changes (new RNFL defect or enlargement of a previous RNFL defect).[13,16–18] In case of disagreement, the participant was not included in the analysis. All CRs were then evaluated by the Laguna ONhE software to estimate ONH Hb, based on colorimetric analysis. Previous studies had described the main characteristics, and the reproducibility of Laguna ONhE.[37,38,40] Succinctly, it is related to analyze CR, in which areas with high levels of hemoglobin reflect red components and regions with low levels reflect better blue and green lights. The optic nerve head (ONH) were divided in 24 sectors (Fig. 1), with the vertical regions, especially sectors 8 and 20, demonstrating the greatest difference in hemoglobin estimation between healthy eyes and those with glaucoma.[37] The ONH Hb analysis, taking into account the usual patterns of localized glaucomatous damage, provides an index: Glaucoma Discriminant Function, a well-established tool for diagnosing the disease. This index varies from −100 to + 85, and the more severe the glaucomatous damage, the more negative its value will be.[37,44–47] More recently, a new index, the Globin Individual Pointer, was incorporated for progression assessment.[42,43]

Data Analysis

Clinical and demographic data were presented by descriptive analysis. Qualitative variables were analyzed by χ^2 tests and presented as frequency distribution. The evaluation of the normal distribution of the data was carried out by Shapiro-Wilk test. Changes in GIP index, which consisted in the difference between baseline and last visit values, were compared between groups (progressors and controls), using event analysis. The area under receiver operating characteristic curves (AUROC) and sensitivity (Se) at fixed specificity (Sp) were calculated. Having in mind the use of the index as a screening tool (first stage) to differentiate between progressors and eyes with stable disease, we focused more specifically on Se evaluation. In

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this context, we set the Sp at 50%, adopting the median of the GIP difference in the stable group as the cutoff value. After that, according to the data related to the progressors group, we considered progression in the presence of values more negative than this chosen cutoff point. Analysis of the performance of the GIP (AUROC and Se), comparing only the progressor group, in relation to changes in NR or RNFL, was also carried out. The MedCalc software (Version 20.110—64 bits; MedCalc Software) was used for computerized statistical analysis, and statistical significance was considered if $P < 0.05$.

RESULTS

Sixty-four glaucoma patients were included in the analysis: 35 progressors (35 eyes) and 29 controls (52 eyes). There was no statistical age difference between progressors and controls (62.2 ± 10.5 and 63.1 ± 14.7 y, respectively; $P = 0.10$). Most of the participants in the study were women (62.5%), with no significant difference in sex distribution between groups ($P = 0.84$). Progressors presented higher mean IOP compared with controls (22.0 ± 5.3 vs. 12.7 ± 3.0 mmHg, respectively, $P < 0.001$). There was a trend for a greater baseline VF damage in progressors, based on VF mean deviation index (-6.9 ± 7.5 vs. -4.2 ± 5.6 dB; $P = 0.08$).

The average time between assessments was 2.9 ± 0.7 years in the progressor group and 2.7 ± 0.5 years in the control group, $P = 0.15$. There was also no statistical difference between progressors and controls, regarding the number of retinographies performed, mean 4.2 ± 1.2 and 3.9 ± 0.9, respectively ($P = 0.27$).

A comparison of Laguna ONhE software parameters (baseline vs. last visit) between progressors and controls are shown in Table 1. The mean baseline GDF was -22.7 ± 25.3 and -21 ± 27.4 in progressors and controls, respectively ($P = 0.76$).

The GIP values at baseline and in the last visit for both groups are represented in Figure 2. A significant change (difference) was found in GIP values in the progressor group ($P < 0.001$). The mean GIP difference over time was -13.0 ± 18.6 in progressors and -2.9 ± 10.4 in controls ($P = 0.001$). Figure 3 demonstrates an example of the Laguna ONhE software analysis of a glaucoma patient classified as a progressor, along with the respective GIP values. Figure 4 shows an example of a patient in the control group and the corresponding GIP values.

According to the type of progression seen in CRs, of the 35 eyes included, 21 showed changes in NR and 14 in RNFL. The GIP values at baseline and in the subsequent assessment related to the group of alterations in NR and RNFL are demonstrated in Figure 5. The mean GIP reduction over time was greater in patients with NR changes (-19.6 ± 19.5 vs. -3.1 ± 12.1; $P = 0.008$).

Analyzing the difference in GIP values in eyes with stable disease, the median value was −3.9. Considering this cutoff value, the GIP was able to correctly identify 69% of the progressors (AUROC of 0.66- Fig. 6A), being 76% of these progressions related to NR changes (AUROC of 0.76- Fig. 6B) and 57% to RNFL changes (AUROC of 0.52- Fig. 6C).

DISCUSSION

The present study analyzed the performance of ONH Hb estimation, through GIP index, in an event analysis of structural progression in glaucoma, showing a good sensitivity. To the best of our knowledge, this is the first study comparing the difference in GIP values, at 2 moments, in glaucoma patients divided into progressors and those with stable disease. Having in mind the low cost, the small number of retinographies that were required and the practicality of this analysis, the software may be useful in clinical practice, as a first-stage assessment for structural progression.

When it comes to disease diagnosis, several previous studies evaluated the estimation of hemoglobin levels in glaucoma.[37–39] Medina-Mesa et al[46] demonstrated significant lower levels of hemoglobin in 121 glaucomatous patients compared with 100 controls. A recent study from our group showed the existence of a significant correlation between GDF values and parameters of both OCT and VF, demonstrating good structure-structure and structure-function relationships.[41] Comparing with the performance of OCT angiography (OCT-A) in discriminating between glaucomatous and healthy eyes, the AUROC was similar for GDF (0.92) and OCT-A circumpapillary capillary vessel density (0.93).[48]

After the diagnosis of glaucoma, the detection of structural progression plays a key role in the adequate monitoring of the disease and patients' prognosis.[24,28,31] To be able to detect progression, a test needs to have good reproducibility and low test-retest variability, thus being useful to separate true progression from noise.[24,32,49,50] Mendez-Hernandez and colleagues evaluated 29 eyes of control and glaucoma patients, with retinographies obtained at different visits and analyzed by 2 examiners. The results, considering all the analyzes, found an intra-class correlation coefficient (ICC) > 0.8 related to the GDF.[40] Gonzalez-Hernandez and colleagues, analyzing 2 retinographies in over 130 participants with and without glaucoma, compared the ICCs between GDF and GIP measurements. The authors reported a greater (better) ICC for GIP values,

TABLE 1. Comparison of Laguna ONhe Software Parameters (Baseline vs. Last Visit) Between Progressors and Controls

	Baseline			Last visit		
	Progressor	**Control**	***P***	**Progressor**	**Control**	***P***
GDF	-22.7 ± 25.3	-21 ± 27.4	0.76	-30.8 ± 27.1	-24.2 ± 28	0.28
GIP	-24.4 ± 35.3	-25.8 ± 31.1	0.84	-37.4 ± 35.3	-28.7 ± 31.5	0.22
Hb amount*	62.1 ± 4.4	61.5 ± 3.9	0.53	61.7 ± 4.1	61.8 ± 3.5	0.93
Hb sector 8	58.1 ± 8.4	59.9 ± 7.8	0.29	56.2 ± 7.9	59.8 ± 7.3	0.03
Hb sector 20	64.1 ± 10.7	59.8 ± 8.4	0.04	62.3 ± 10.1	60 ± 8.8	0.27

Data are represented as mean ± deviation.
*Total hemoglobin amount.
GDF indicates Glaucoma Discriminant Function; GIP, Globin Individual Pointer; Hb, hemoglobin.

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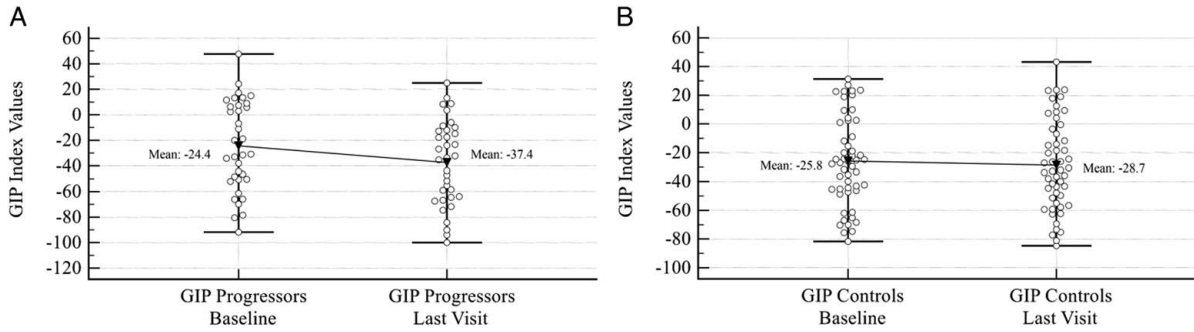

FIGURE 2. Distribution of GIP index values, comparing baseline assessment with the last visit. A, Progressor group, (B) group of eyes with stable disease (controls). GIP indicates Globin Individual Pointer.

suggesting that the GIP would be a more suitable parameter for individual progression evaluation.[43] In fact, the GIP has been considered a metric that allows longitudinal changes to be assessed, due to its greater reproducibility and stability.[42]

As aforementioned, in this study, the difference in GIP values was evaluated between 2 retinographies. Nonetheless, Gonzalez-Hernandez and colleagues found that analyzing a greater number of images, progression detection can increase. Evaluating 743.696 images from a large database, Retisalud, from the Canary Islands Health Service, especially in cases with lower GDF values, the GIP detected progression in 2.59% of cases with 4 examinations, but up to 42.6% with 14 examinations.[42] Even though these numbers highlight the importance of large amounts of examinations for progression assessment over time, this is not always feasible in clinical practice, especially due to time of follow-up itself. In many occasions patients are being followed for only 2 years, and even so clinicians need some information on progression, likely based on a small number of serial tests.

We believe that the best performance demonstrated by NR changes is closely related to the method itself carried out by the Laguna ONhE software. It divides the head of the ONH, taking into account the vessels in this region, in

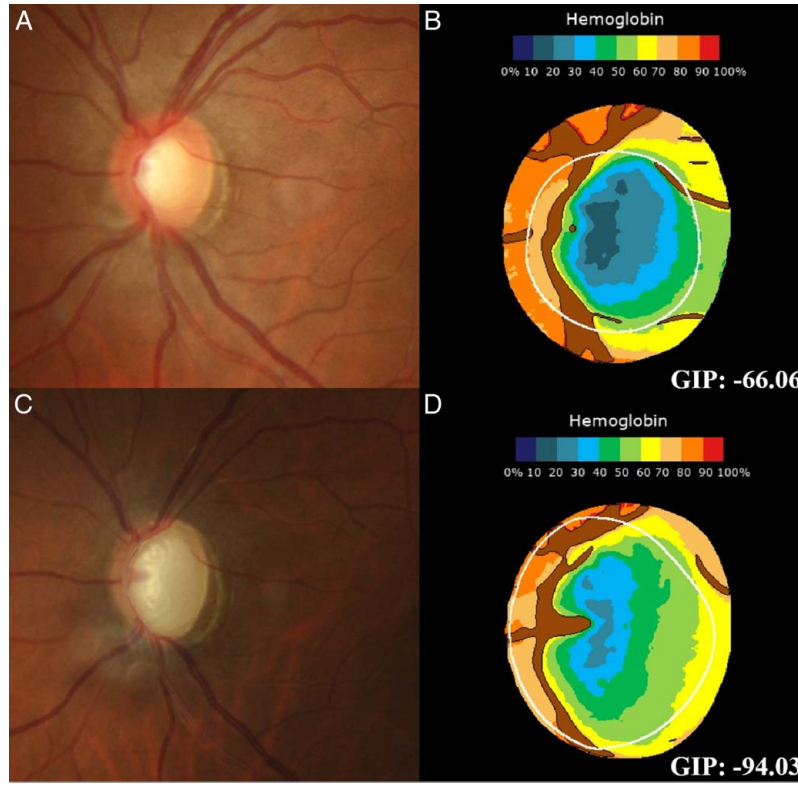

FIGURE 3. A, Color retinography of the optic disc of patient with glaucoma, (B) correspondent pseudo-image estimating the amount of hemoglobin (according to the colorimetric scale shown) and the correspondent Globin Individual Pointer (GIP) index of –66.06. C, Color retinography of the optic disc of the same patient, demonstrating marked changes in the neuroretinal rim, confirming structural progression. D, Correspondent pseudo-image estimating the amount of hemoglobin, demonstrating changes and worsening of values, in accordance with the color scale shown, and declining of GIP values to –94.03. Figure 3 can be viewed in color online at www.glaucomajournal.com.

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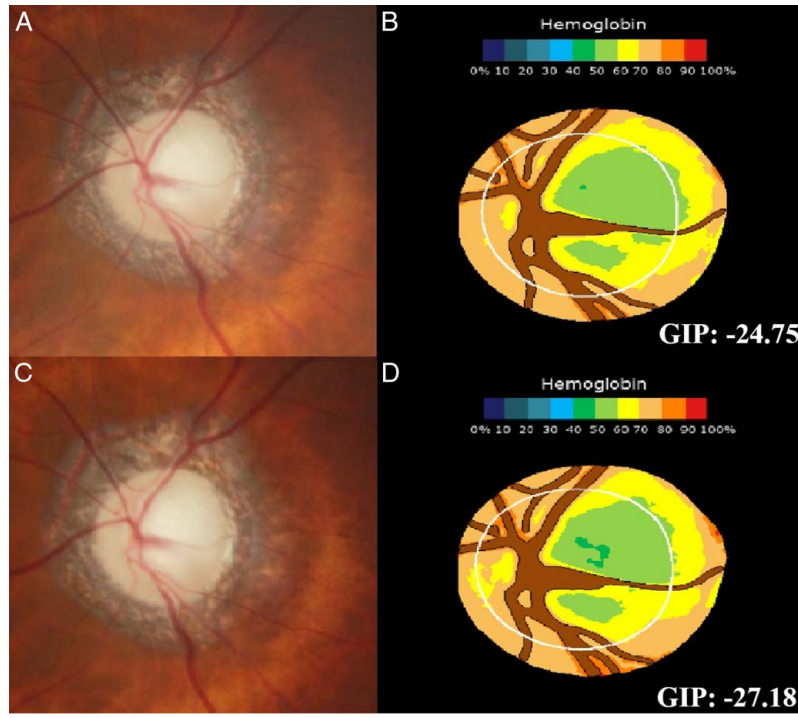

FIGURE 4. A, Color retinography of the optic disc of patient with stable disease (control), (B) correspondent pseudo-image estimating the amount of hemoglobin (according to the colorimetric scale shown) and the correspondent GIP index of −24.75. C, Color retinography of the optic disc of the same patient, not demonstrating structural changes. D, Correspondent pseudo-image estimating the amount of hemoglobin, demonstrating GIP values of −27.18. GIP indicates Globin Individual Pointer. Figure 4 can be viewed in color online at www.glaucomajournal.com.

estimating hemoglobin values. The software does not directly analyze the structures and consequently the changes present in the RNFL.[37,38]

It is important to highlight the main clinical implications of this study. Detecting structural progression in glaucoma can be a challenging situation in clinical practice.[32,33] Although the use of OCT adds a lot to this condition, it has the disadvantages of high cost, the no-portable aspect of the tool, the need for examinations to be carried out on identical devices to analyze progression and worse performance on optical discs with a challenging appearance, such as in high myopia.[22,23,30,31] In this context, the use of a low-cost and easy to use software, based on simple retinographies, could contribute to detection of progression.[37,38] The fact that the software can be performed on previous (old) retinographies, is particularly interesting for glaucoma suspects or glaucoma patients who are initiating a new follow-up on a different facility. We know that in these situations the structural follow-up based on OCT is usually reseted, due to lack of interchangeability between devices. Another advantage is that the speed of analyzing the retinography and providing the indices, takes ~4 seconds.[37,41] Finally, event analysis, as performed in this study, can contribute to a first-stage evaluation, and in suspected cases of progression, patients should undergo a deeper assessment for confirmation. Therefore, in an easier and more accessible way, suspicion of disease progression can be increased.

Some specific limitations of this study need to be addressed. First, bias that may occur in cross-sectional

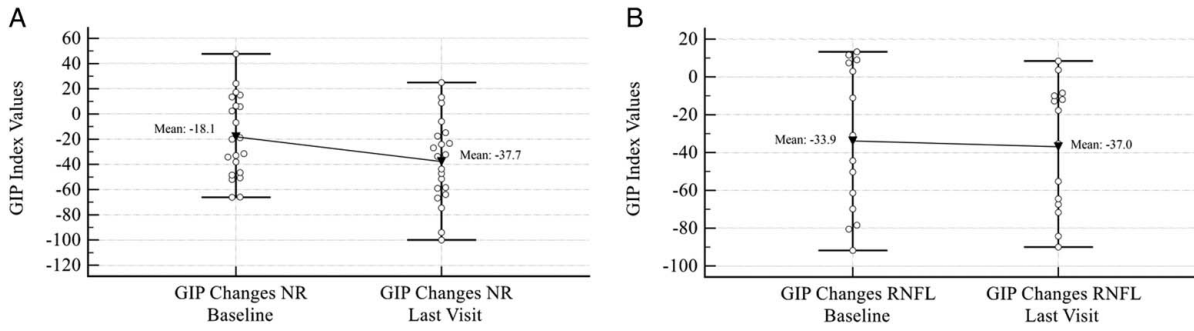

FIGURE 5. Distribution of GIP index values, comparing baseline assessment with the last visit, in the progressor group. A, Related to changes in NR. B, Related to changes in RNFL. GIP indicates Globin Individual Pointer; NR, neuroretinal rim; RNFL, retinal nerve fiber layer.

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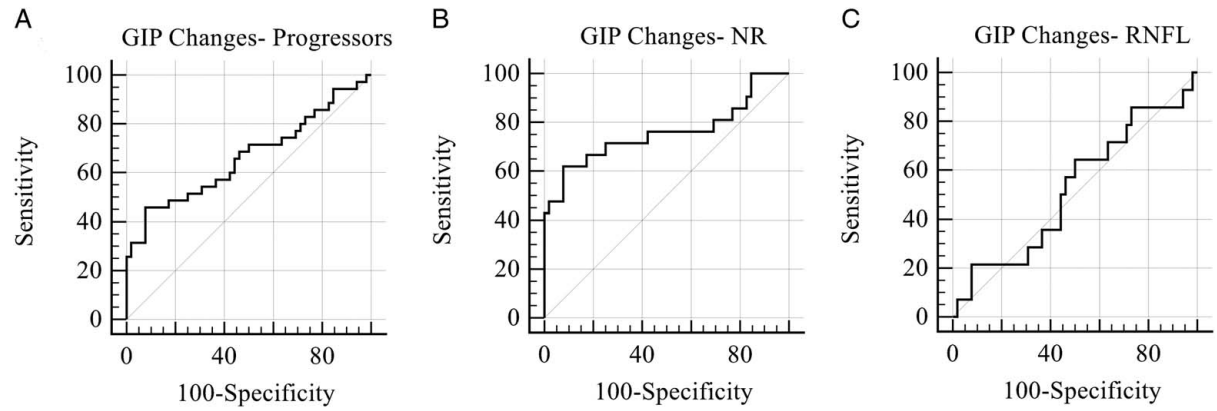

FIGURE 6. Areas under receiver operating characteristic curves in detecting structural progression of glaucoma, considering GIP changes. A, Progressor group (0.66), (B) related to changes in neuroretinal rim (NR—0.76), (C) related to changes in retinal nerve fiber layer (RNFL—0.52). GIP indicates Globin Individual Pointer.

studies must be taken into account. Second, examiners only had access to retinography, and not the clinical information or the evolution of visual field and OCT parameters to detect progression. However, they are extremely experienced glaucoma examiners, and at any sign of doubt, the patient was not included in the study. Third, as in most cases glaucoma represents a slowly progressive disease, we considered a relatively short 2-year follow-up to detect changes. Furthermore, considering that the software aims to estimate the hemoglobin level, systemic pathologies such as high blood pressure and diabetes could interfere with the results. However, a previous study by our group, did not demonstrated differences in GDF values in patients with glaucoma and controls.[41] Finally, the results should not be extrapolated to populations other than the study sample, as patients with high myopia, who were not included.

In conclusion, automated estimation of ONH Hb, through the GIP index of the Laguna ONhE software, demonstrated good sensitivity to differentiate progressors from stable glaucoma patients. This type of analysis seems to perform better in cases in which progression was documented based on structural changes of the neuroretinal rim, rather than on RNFL changes. Overall, even though using a small number of CRs (2), event analysis based on GIP changes over time can be useful as a screening tool to evaluate structural progression. We believe that positive cases should undergo a deeper assessment for confirmation. Further studies evaluating the GIP index using a larger number of CRs, based on trend analysis, are warranted, and currently being carried out by our group.

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