Abilities of circumpapillary retinal nerve fiber layer thickness and vascular density to discriminate stages in primary open-angle glaucoma

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Key messages

What is known:

- Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) determined by optical coherence tomography (OCT) reaches a floor where further thinning cannot be detected if glaucoma is moderate to severe, whereas circumpapillary vessel density (cpVD) determined by OCT-angiography is less affected by the floor effect, even in severe cases. The differences in the ability of cpRNFLT and cpVD to discriminate glaucoma severities and to estimate visual field are unknown.

What is new:

- The ability to distinguish between moderate and severe glaucoma was higher for cpVD. cpVD is better for follow-ups after moderate stage.
- The mean absolute error in estimating the visual field from both cpRNFLT and cpVD was significantly less than the error from cpRNFLT alone. The combination of cpRNFLT and cpVD may improve visual field estimation.

Abstract

Purpose: To clarify the abilities of circumpapillary retinal nerve fiber layer thickness (cpRNFLT) obtained by optical coherence tomography (OCT) and circumpapillary vessel density (cpVD) measured by OCT-angiography to distinguish different stages in primary open-angle glaucoma determined by 24-2 or 30-2 static visual field (VF) testing.

Methods: This retrospective study includes 25 healthy normal eyes of 25 subjects and 87 primary open-angle glaucoma eyes of 87 patients. Areas under the receiver operating characteristic curves (AUROC) were evaluated for determining glaucoma stages using cpRNFLT and cpVD. The absolute errors of the estimated mean total deviation (mTD) using optimal models with cpRNFLT and cpVD were also compared.

Results: The AUROCs for discriminating glaucomatous eyes from normal eyes was significantly higher for cpRNFLT than the respective AUROCs for cpVD (0.969 [95% CI 0.939 to 0.998] vs. 0.872 [95% CI 0.806 to 0.938], p = 0.006), whereas cpVD had significantly higher AUROC for discriminating severe glaucoma eyes from moderate glaucoma eyes than cpRNFLT (0.771 [95% CI 0.655 to 0.886] vs. 0.578 [95% CI 0.420 to 0.736], p = 0.022). The mean absolute error in estimating mTD using both cpRNFLT and cpVD was significantly less than the error using cpRNFLT alone (4.56 ± 3.76 dB

vs. 5.39 ± 4.00 dB, p = 0.027).

Conclusion: Our results suggest that cpVD is better for follow-ups after moderate stage. The combination of cpRNFLT and cpVD may improve VF estimation compared to cpRNFLT alone.

Keywords

Glaucoma; OCT; OCT angiography; cpVD; cpRNFLT

Introduction

Glaucoma causes progressive visual field (VF) damage, which can significantly impact patient quality of life [1]. Because VF testing is subjective, fluctuations in results or difficulties in conducting the test often arise [2]. Therefore, objective measurements, which can accurately estimate glaucomatous VF defects, are essential. Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) measured using optical coherence tomography (OCT) is a valuable glaucoma diagnostic tool [3, 4]. Reductions in cpRNFLT correlate well with the degree of glaucomatous VF damage, especially in the early stages of glaucoma [5]. However, the use of cpRNFLT in the clinic is problematic. Progression of severe glaucoma is difficult to detect due to the “floor effect” [6-8], which is observed in measurements with limited dynamic ranges. For instance, in the severe stages of glaucoma, the actual progression of glaucoma may be misinterpreted as stability because cpRNFLT has reached the measurement range floor. Thus, measurement of cpRNFLT by OCT may be valuable in the early stages of glaucoma but not in the severe stages.

Circumpapillary vessel density (cpVD) measured by OCT angiography (OCTA) may be useful[9] for monitoring severe glaucoma because cpVD is less likely to suffer from a floor effect than cpRNFLT [10, 11]. Conversely, the diagnostic performance of

cpVD in early glaucoma is controversial; some reports demonstrate that cpVD is equivalent to cpRNFLT, while others report that cpVD is inferior to cpRNFLT [12-14].

Thus, the diagnostic ability and characteristics of cpRNFLT and cpVD at different glaucoma stages are controversial. Additionally, few comparative studies have examined the ability of cpRNFLT and cpVD to estimate VF defects [15, 16]. The purpose of this study was to compare the discriminating performance of cpRNFLT and cpVD at each stage in eyes with primary open-angle glaucoma (POAG) and normal eyes and evaluate the ability of cpRNFLT and cpVD to estimate VF damage.

Methods

This retrospective, observational comparative, single-center study was conducted in adherence to the tenets of the Declaration of Helsinki. The procedures were approved by the Institutional Review Board and the Ethics Committee of the Nagoya University Graduate School of Medicine. The institutional review board exempted this study from informed consent due to the retrospective study design. We published the study protocol on the website and offered participants the opportunity to opt out. The medical records of all patients who were diagnosed solely with POAG and consecutive patients with normal eyes who underwent routine eye examinations and had no ocular disease except for cataract or a history of vitreous disease such as epiretinal membrane or

retinal break in the opposite eye were evaluated. Patients who were examined within six months for OCT, OCTA, and VF at the Nagoya University Hospital from February 2017 to November 2021 were included in the study as a convenience sample. The Standards for Reporting of Diagnostic Accuracy Studies (STARD) checklist for this study is shown as a supplementary information.[17]

Glaucoma specialists (KY and RT) classified normal eyes and POAG eyes while being blinded to the clinical information of the eyes, except for the parameters used in the following criteria. The criteria for normal eyes were: (1) normal findings in slit-lamp and ophthalmoscopic examinations; (2) best-corrected visual acuity (BCVA) better than 20/25; (3) intraocular pressure (IOP) ≤ 21 mmHg; and (4) normal VF of the Anderson–Patella classification; (5) age >20 years. The criteria for eyes with POAG included: (1) the presence of glaucomatous optic disc changes determined by biomicroscopy, VF defects, and abnormal cpRNFL thinning determined by Cirrus OCT with embedded software, (2) open-angle determined by gonioscopy, and (3) age >20 years. Eyes in the POAG group were classified into three groups according to the degree of VF impairment: early, mean deviation (MD) > −6 dB; moderate, −12 dB < MD < −6 dB; and severe, MD < −12 dB. The VFs were determined using a Humphrey Field Analyzer II (HFA; Carl Zeiss Meditec AG, Jena, Germany) and the Swedish interactive

threshold algorithm standard central 24-2 and 30-2 program. The mean total deviation of common 58 points of both 24-2 and 30-2 VF tests was recorded as an objective measure of the VF and expressed as mean total deviation (mTD). Only reliable VF tests were used; examinations with 20% fixation errors and > 33% false-positives or false-negatives were excluded.

Exclusion criteria

Patients with a history of systemic or ocular disease affecting the blood flow or structure of the retina were excluded from the study. In addition, eyes with severe cataracts or high myopia (axial length longer than 27 mm) were excluded. Eyes with IOP > 21 mm Hg on the test day were also excluded because high IOP may affect the measurement of cpVD[18, 19].

Measurements of clinical parameters

All subjects underwent ophthalmologic and general examinations that included the following: slit-lamp and ophthalmoscopic examinations, gonioscopy, IOP measurements, perimetry, spectral domain-OCT (SD-OCT) examinations, and swept source-OCTA (SS-OCTA) examination within six months. The decimal BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analyses. The axial lengths were measured using partial optical coherence interferometry (IOL Master; Carl Zeiss Meditec, La Jolla, CA). The IOP was measured

with a handheld tonometer (Icare; Tiolat Oy, Helsinki, Finland).

Measuring circumpapillary retinal nerve fiber layer thickness

The global cpRNFLT was measured using the manufacturer's software with a SD-OCT system (CIRRUS HD-OCT 5000, Carl Zeiss AG, German). Poor quality images caused by artifacts, poor centration, and signal strength < 7 were excluded from the analyses.

Measurement of circumpapillary vessel density

Microcirculation images were obtained by the SS-OCTA system (Plex Elite 9000, Carl Zeiss AG, German). The global cpVD in the peripapillary nerve fiber layer within a 6-mm diameter circle centered on the optic papilla was calculated by the instrument software and prototype analysis vessel density quantification software (Peripapillary Nerve Fiber Layer Microvasculature Density v0.10, ARI Network Hub, Carl Zeiss Meditec Inc., Dublin, CA, USA) supplied by the manufacturer. The central region within a 6mm diameter circle, specifically a 2mm diameter area at the center, was excluded from the measurement, and major vessels were also excluded. Low-quality images, images with the center of the image misaligned with the optic disc, and images with signal strength < 7 were excluded.

Statistical Analysis

All data are reported as means ± standard deviation (SD) unless otherwise specified. One eye was randomly selected if data existed for both of the patient's eyes. Baseline

characteristics were compared using the one-way ANOVA. Scatterplots for cpRNFLT and cpVD were compared with scatterplots for mTD. The linear splines were expressed with locally weighted scatterplot smoothing (LOWESS) curves. Receiver operating characteristic (ROC) curves were drawn based on a logistic regression analysis of the ability of cpRNFLT and cpVD to differentiate between normal eyes and the different stages of glaucoma. The area under the receiver operating characteristic curves (AUROC) were compared between cpRNFL and cpVD using the Delong test. Single or multiple regression analyses with leave-one-out cross-validation were conducted to estimate mTD based on cpRNFLT and/or cpVD. Each model was trained on all eyes except one eye as test data. When the model was adapted to the test data, the estimated value was determined and repeated to obtain the estimated value for all patients included in the study. The absolute error was defined as the absolute difference between the actual mTD and estimated mTD calculated using the regression model obtained with leave-one-out cross-validation. The absolute errors in cpRNFL and/or cpVD were compared using the one-way ANOVA and the Tukey test for multiple comparisons. The statistical programming language R (V.4.1.2, The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. A p-value < 0.05 was considered statistically significant.

Results

Data were obtained from 43 eyes of 34 healthy subjects and 223 eyes of 133 glaucoma patients. After excluding eyes that did not meet the criterion and randomly selecting one eye if two eyes were included per patient, a total of 112 eyes from 112 subjects were analyzed (Figure 1), including 25 eyes from 25 healthy subjects, 24 eyes with early glaucoma from 24 patients, 22 eyes with moderate glaucoma from 22 patients, and 41 eyes with severe glaucoma from 41 patients. Table 1 shows the baseline clinical characteristics of the study subjects. There were significant differences in visual acuity, IOP, MD, and mTD values among severity levels. The cpRNFLTs obtained by SD-OCT were 93.7 ± 9.5 μm for normal eyes, 74.4 ± 9.5 μm for eyes with early glaucoma, 67.5 ± 11.4 μm for eyes with moderate glaucoma, and 63.5 ± 7.7 μm for eyes with severe glaucoma (Table 2). The cpRNFLTs of any glaucoma severity were significantly less than the cpRNFLT of normal eyes (all, $p < 0.001$). The cpRNFLT of eyes with severe glaucoma was significantly less than the cpRNFLT of eyes with early glaucoma ($p < 0.001$). The cpVDs obtained by SS-OCTA were 54.7 ± 1.4% in normal eyes and 52.4 ± 2.6%, 52.0 ± 2.4%, and 49.0 ± 3.4% in eyes with early, moderate, and severe glaucoma, respectively, and these cpVDs were significantly lower than that of

192 normal eyes (all, $p < 0.001$). The cpVD of eyes with severe glaucoma was significantly
193 lower than the cpVDs of eyes with early and moderate glaucoma (all, $p < 0.001$).
194 The AUROC based on logistic regression analysis discriminating all eyes with
195 glaucoma from normal eyes by cpRNFLT (0.969, 95% CI: 0.939–0.998) was
196 significantly higher than the AUROC for the cpVD (0.872, 95% CI: 0.806–0.938, $p =$
197 0.006; Figure 2A, Table 3). The AUROC discriminating eyes with early glaucoma from
198 normal eyes by cpRNFLT (0.929, 95% CI: 0.844–1.000) was higher than the AUROC
199 for cpVD (0.783, 95% CI: 0.654-0.913), but not significantly ($p = 0.073$; Figure 2B).
200 AUROCs discriminating eyes with moderate glaucoma from eyes with early glaucoma
201 using cpRNFLT (0.710, 95% CI: 0.552–0.869) and cpVD (0.576, 95% CI: 0.405–0.747)
202 were not significantly different (Figure 2C). The AUROC discriminating eyes with
203 severe glaucoma from eyes with moderate glaucoma using cpVD (0.771, 95% CI:
204 0.655–0.886) was significantly higher than the AUROC using cpRNFLT (0.578, 95% CI:
205 0.420–0.736, $p = 0.022$; Figure 2D).
206 Figure 3 shows the relationship between mTD and cpRNFLT and cpVD in all
207 eyes. It was found that cpRNFLT and cpVD were significantly correlated with mTD ($r =$
208 0.635; $p < 0.001$ and $r = 0.657$; $p < 0.001$, respectively) in all eyes. In normal eyes and
209 eyes with early and moderate glaucoma, cpRNFLT significantly correlated with mTD (r

= 0.598, p < 0.001). However, no significant correlation was observed between cpRNFLT and mTD for eyes with severe glaucoma (r = 0.203, p = 0.204). On the other hand, a significant correlation was detected between cpVD and mTD in normal eyes and eyes with early and moderate glaucoma (r = 0.377, p = 0.001) and also in eyes with severe glaucoma (r = 0.417, p = 0.007).

The mean absolute error calculated using the regression model with both cpRNFLT and cpVD (4.56 ± 3.76 dB) was significantly less than the absolute error calculated with cpRNFLT only (5.39 ± 4.00 dB, p = 0.027; Figure 4), but not significantly less than the absolute error calculated with cpVD only (5.17 ± 4.08 dB, p = 0.142). The model for estimating mTD from all cases with both cpRNFLT and cpVD is as follows: mTD = −84.4 + 1.12 × cpVD (Standard Error [SE] = 0.188, p < 0.001) + 0. 233 × cpRNFLT (SE = 0.0435, p < 0.001). The model for estimating mTD from all cases with cpRNFLT alone is: mTD = −36.4 + 0.367 × cpRNFLT (SE = 0.0426, p < 0.001). The model for estimating mTD from all cases with cpVD alone is: mTD = −94.3 + 1.65 × cpVD (SE = 0.180, p < 0.001).

Discussion

In this study, we examined the ability of cpRNFLT and cpVD to distinguish stages of glaucoma. The AUROCs using cpVD were significantly better at discriminating between

moderate and severe glaucoma. In eyes with severe glaucoma, cpVD significantly correlated with mTD, whereas cpRNFLT did not correlate with mTD. The mean absolute error in estimating mTD using both cpRNFLT and cpVD was significantly less than the error using cpRNFLT alone.

The relationship between cpVD and VF damages has been described in previous reports [9, 20, 21]. Several reports indicate that the abilities of cpVD and cpRNFLT to diagnose early glaucoma are similar, while other reports indicate that cpRNFLT is better at diagnosing early glaucoma [12, 22, 23]. In this study, the AUROC for differentiating eyes with early glaucoma from normal eyes using cpVD (0.872) was not significantly but lower than the AUROC for cpRNFL (0.969). The AUROC values for cpVD in previous reports vary but were roughly consistent with the values in the present study [12, 13, 22]. Lee et al. suggested that the primary change in early glaucoma is a decrease in cpRNFLT, and the decrease in cpVD may be a secondary change, which may explain the superiority of cpRNFL in diagnosing early glaucoma [24]. However, whether nerve dropout or reduced blood flow comes first in glaucoma is still controversial. In contrast, the discriminating performance of cpRNFLT is inferior in severe glaucoma relative to early glaucoma due to the floor effect [25]. In this study, the AUROC differentiating eyes with severe glaucoma from eyes with moderate

247 glaucoma using cpRNFLT was significantly lower than the AUROC using cpVD. To our
248 knowledge, no reports compare the ability of cpVD and cpRNFLT to discriminate
249 between eyes with moderate and severe glaucoma. However, the lack of a floor effect
250 in cpVD until the disease is more severe is reasonable. Phillips et al. reported that
251 cpRNFLT obtained by OCT floored earlier (MD: -17.8dB) than the peripapillary vessel
252 density obtained by OCTA (MD: -26.6dB) [11]. Moghimi et al. also indicated the
253 superiority of OCTA with respect to the floor effect. In the study, cpRNFLT reached the
254 floor at an MD value of -17.5 dB, while no floor was detected in cpVD [10]. Additionally,
255 cpRNFLT did not significantly correlate with mTD in cases of severe glaucoma,
256 whereas cpVD significantly correlated with mTD even in cases of severe glaucoma.
257 The difference between these two correlations may be due to the floor effect [26]. The
258 results of this study suggest that cpVD is better for follow-ups after the moderate stage.
259 Therefore, the difference in efficacy between cpRNFLT and cpVD depending on the
260 severity of glaucoma is useful for understanding the function versus structure
261 relationship in glaucoma.
262 The absolute error between the actual mTD and the estimated mTD from the
263 regression model using both cpRNFLT and cpVD was significantly less than the error
264 using cpRNFLT values alone. This result suggests that the combination of cpRNFLT

and cpVD may be more effective in estimating glaucomatous VF defects than cpRNFLT only. Several studies have attempted to predict glaucomatous VF damage from structure using cpRNFLT [27-30]. But only a few studies have used OCTA [16, 31]. Wong et al. reported that combining OCT and OCTA improves the modeling of local VF defects in early glaucoma [31]. To the best of our knowledge, this is the first study to predict VF from OCT and OCTA parameters, including many severe cases. However, the mean absolute error between the predicted mTD and actual mTD values was relatively large in this study. The large errors may be because of using the image of the whole area around the optic disc for estimating VF and including many eyes with severe glaucoma and a small number of cases relative to previous studies. Further research should be conducted to find a more appropriate estimation model using the combination of cpRNFLT and cpVD.

There are several limitations to this study. First, this study excluded highly myopic eyes. Shin et al. reported that the cpVD correlates better with VF than cpRNFLT in patients with glaucoma and high myopia [32]. Further studies of diagnostic performance in high myopia are needed. Second, only one VF and imaging test was performed. In addition to the variability in the VF test results, cpRNFLT and cpVD may also vary due to changes in image quality and

physiological blood flow. Especially, the variability of the results of them in moderate to severe glaucoma may be significant. Thus, we defined exclusion criteria for VF testing and images to avoid this effect as much as possible. Third, this study is based on the image of the whole area around the optic disc and the global VF. The cpRNFL and cpVD of the nasal retina, which are less affected by VF measurement points, are also measured in the same way as the more critical temporal retina. A more detailed sectoral study corresponding to the VF may be needed. Fourth, the OCT, OCTA, and VF measurements in this study were performed within 6 months. Therefore, if visual field or structural disorders progress during this time, there may be a discrepancy in the results. Fifth, thinning of the cpRNFL by OCT was used as a selection criterion for eyes with glaucoma. This may lead to incorporation bias in tests such as diagnostic ability. This bias may overestimate the sensitivity, specificity, and AUC of cpRNFLT in tests where cpRNFLT distinguishes between severities, especially in distinguishing between normal eyes and all eyes with glaucoma, and between normal eyes and eyes with early glaucoma. The superiority of cpRNFLT over cpVD in distinguishing between normal eyes and all eyes with glaucoma and between normal eyes and eyes with early glaucoma may be also overestimated.

In conclusion, cpVD was superior in distinguishing between moderate and severe glaucoma. The mean absolute error of the estimated mTD based on the combination of cpRNFLT and cpVD was significantly less than the absolute error using cpRNFLT alone, suggesting that the complementary use of the two measurements may be useful in estimating the severity of glaucoma.

Compliance with Ethical Standards

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Competing interests: KY, None; RT, None; YK, None; KK received honoraria for lectures from Senju; RA, None; HT received non-financial research support from Carl Zeiss related to swept source optical coherence tomography and grants and honoraria for lectures from Otsuka, Kowa, Santen, Senju, Sanofi, Alcon, Novartis, ROHTO, and Wakamoto. She received grants and consulting fees from Bayer and honoraria for lectures from HOYA and Johnson & Johnson; TI, None; KN received grants from Takara bio, Takeda pharmaceutical, JCR Pharma, Alcon, and Bayer, and honoraria for lectures from Novartis, Santen, Chugai Pharma, Kowa, Senju, Otsuka, and Wakamoto. He has a patent related to a single AAV vector.

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Standards of reporting: The Standards for Reporting of Diagnostic Accuracy Studies (STARD) checklist for this study is shown as a supplementary information.[17]

Ethical approval: This study was conducted in adherence to the tenets of the Declaration of Helsinki. The procedures were approved by the Institutional Review Board and the Ethics Committee of the Nagoya University Graduate School of

Medicine.

Informed consent: The institutional review board exempted this study from informed consent due to the retrospective study design. We published the study protocol on the website and offered participants the opportunity to opt out.

Author Contributions: KY, RT, TI and KN were involved in the design and conduct of the study; KY, RT, and TI were involved in the collection, management, analysis, and interpretation of data; and KY, RT, KK, RA, HT, TI, and KN were involved in the preparation, review, and approval of the manuscript.

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Table 1. Demographics of subjects.

	Control	POAG			*p*-value
		early	moderate	severe	
Number of eyes	25	24	22	41	
Sex, m/f	14 / 11	14 / 12	13 / 9	30 / 11	
Age, year	68.8 ± 11.2	67.6 ± 11.7	69.2 ± 12.1	69.3 ± 11.0	0.950
Axial length, mm	24.6 ± 0.9	24.9 ± 1.1	24.7 ± 1.2	24.9 ± 1.5	0.561
Visual acuity, logMAR	0.034 ± 0.076	0.039 ± 0.143	0.133 ± 0.174	0.199 ± 0.311	0.007
Intraocular pressure, mmHg	14.4 ± 2.9	12.1 ± 3.5	11.1 ± 4.1	12.3 ± 4.1	0.023
Mean deviation, dB	-0.12 ± 1.23	-2.87 ± 1.77	-9.32 ± 1.84	-19.6 ± 5.5	< 0.001
Mean total deviation, dB	-0.20 ± 1.34	-2.88 ± 1.88	-9.16 ± 1.73	-19.0 ± 5.2	< 0.001

MAR, minimum angle of resolution; POAG, primary open-angle glaucoma

Table 2. Values of cpRNFLT and cpVD in normal eyes and each stage of glaucoma.

	Control	POAG			*p*-value
		early	moderate	advanced	
Number of eyes	25	24	22	41	
cpRNFLT, μm	93.7 ± 9.5	74.4 ± 9.5	67.5 ± 11.4	63.5 ± 7.7	< 0.001
cpVD, %	54.7 ± 1.4	52.4 ± 2.6	52.0 ± 2.4	49.0 ± 3.4	< 0.001

POAG, primary open-angle glaucoma; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; cpVD, circumpapillary vessel density

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Table 3. The area under the receiver operating characteristic curve of discriminating each stage of glaucoma.

	cpRNFLT		cpVD		*p*-value
	AUROC	95% CI	AUROC	95% CI	
normal (25 eyes) vs. glaucoma (87 eyes)	0.969	0.939–0.998	0.872	0.806–0.938	0.006
normal (25 eyes) vs. early glaucoma (24eyes)	0.929	0.844–1.000	0.783	0.654–0.913	0.073
early (24 eyes) vs. moderate glaucoma (22 eyes)	0.710	0.552–0.869	0.576	0.405–0.747	0.206
moderate (22 eyes) vs. severe glaucoma (41 eyes)	0.578	0.420–0.736	0.771	0.655–0.886	0.022

cpRNFLT, circumpapillary retinal nerve fiber layer thickness; cpVD, circumpapillary

vessel density; AUROC, area under the receiver operating characteristic curve

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Figure Legends

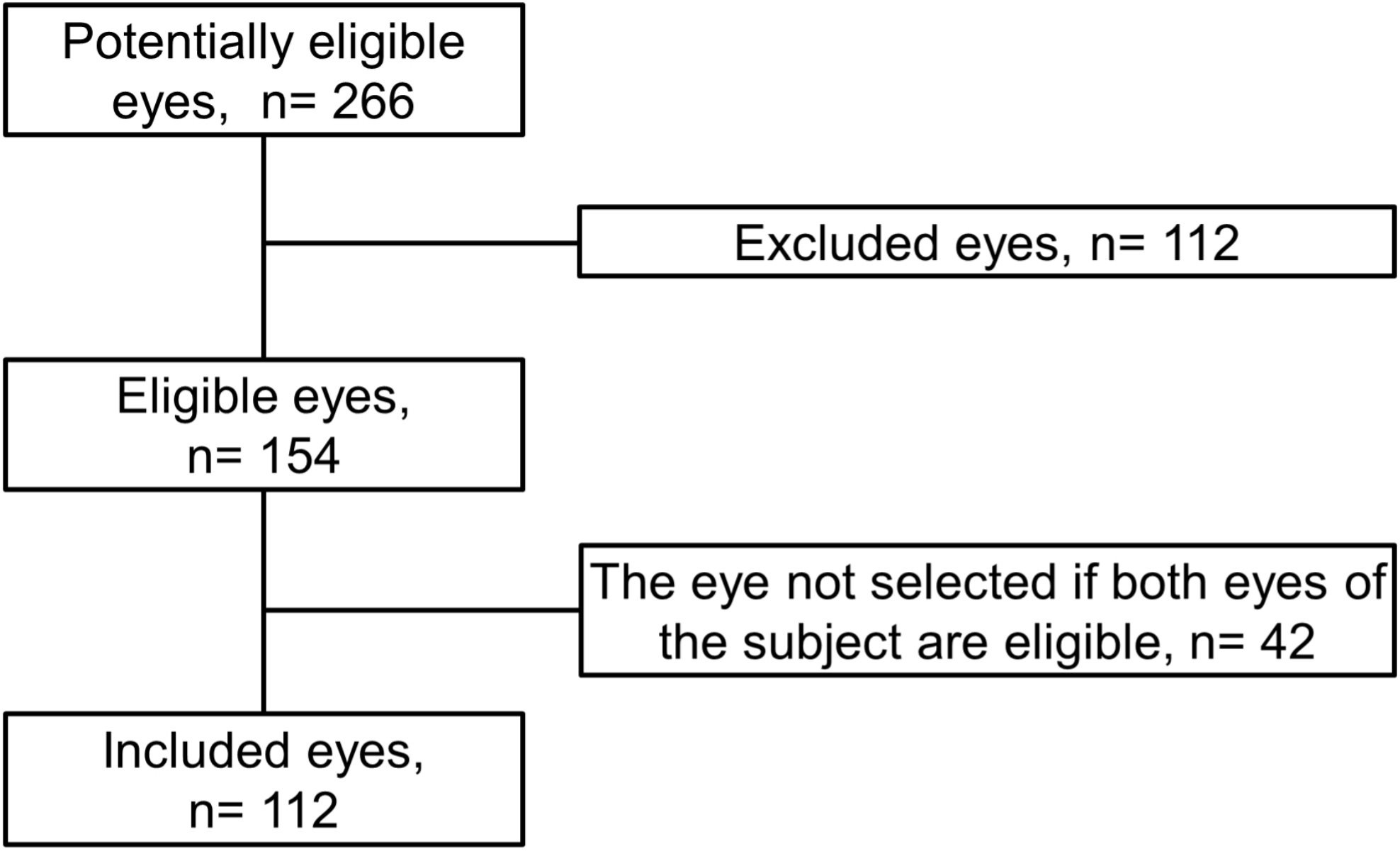
Figure 1 Study subjects flow chart.

Figure 2 Receiver operating characteristic (ROC) curves of cpRNFLT and cpVD for discriminating each stage of glaucoma. (**A**) ROC curves for discriminating all eyes with glaucoma from normal eyes. The areas under the ROCs (AUROCs) were 0.969 (95% confidence interval (CI) 0.939–0.998) for cpRNFLT and 0.872 (95% CI 0.806–0.938) for cpVD (p = 0.006). (**B**) The ROC curves for discriminating eyes with early glaucoma from normal eyes. The AUROCs were 0.929 (95% CI 0.844–1.000) for cpRNFLT and 0.783 (95% CI 0.654–0.913) for cpVD (p = 0.073). (**C**) The ROC curves for discriminating eyes with moderate glaucoma from eyes with early glaucoma. The AUROCs were 0.710 (95% CI 0.552–0.869) for cpRNFLT and 0.576 (95% CI 0.405–0.747) for cpVD (p = 0.206). (**D**) The ROC curves for discriminating severe glaucoma eyes from moderate eyes. The AUROCs were 0.578 (95% CI 0.420–0.736) for cpRNFLT and 0.771 (95% CI 0.655–0.886) for cpVD (p = 0.022). cpRNFLT: circumpapillary retinal nerve fiber layer thickness; cpVD: circumpapillary vessel density

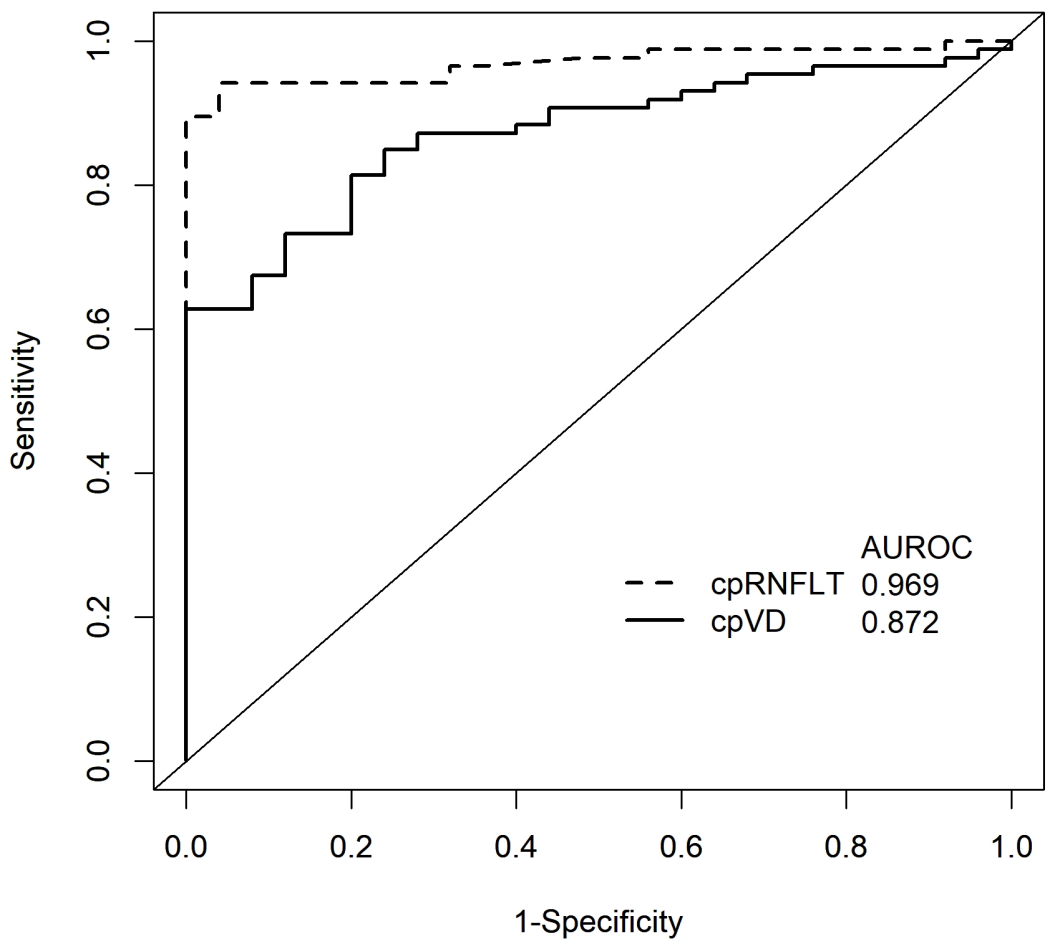
Figure 3 Scatterplots with locally weighted scatterplot smoothing curves showing the relationship between mean total deviation (mTD) and cpRNFLT (**A**) and cpVD (**B**). With more severe mTD, cpRNFLT showed little change with decreasing mTD, but cpVD did not show changes. Between cpRNFLT and mTD, a significant correlation was detected in normal eyes and eyes with early and moderate glaucoma (r = 0.598, p < 0.001), but no significant correlation was detected in eyes with severe glaucoma (r = 0.203, p = 0.204). Between cpVD and mTD, a significant correlation was detected in normal eyes and eyes with early and moderate glaucoma (r = 0.377, p = 0.001) and in eyes with severe glaucoma (r = 0.417, p = 0.007).

cpRNFLT: circumpapillary retinal nerve fiber layer thickness; cpVD: circumpapillary vessel density

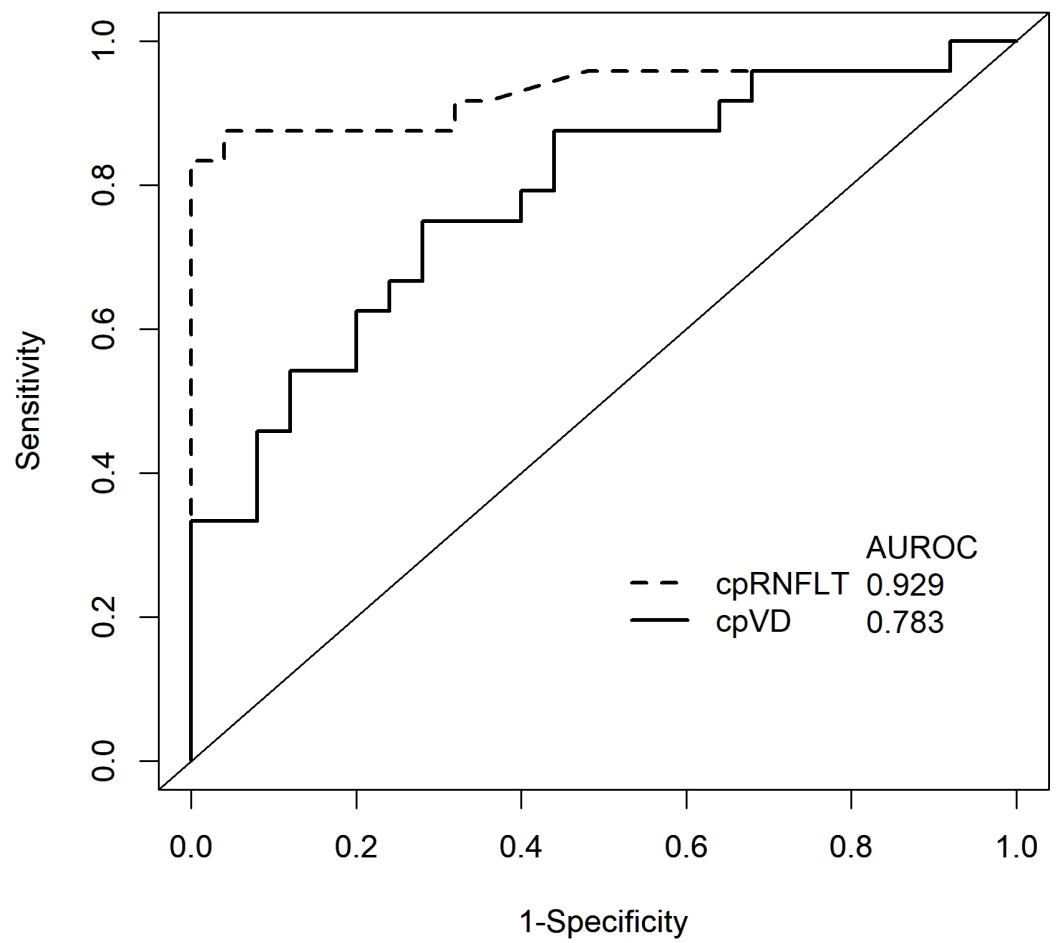
Figure 4 Box plots comparing the absolute errors between the mean total deviation (mTD) estimated from cpRNFLT and/or cpVD and the actual mTD. The mean absolute error with both cpRNFLT and cpVD (4.56 ± 3.76 dB) was significantly less than that with cpRNFLT sorely (5.39 ± 4.00 dB, $p = 0.027$) and not significantly less than that with cpVD sorely (5.17 ± 4.08 dB) ($p = 0.142$). The model for estimating mTD from all cases with both cpRNFLT and cpVD is as follows: mTD = -84.4 + 1.12 × cpVD (standard error (SE) = 0.188, $p < 0.001$) + 0.233 × cpRNFLT (SE = 0.0435, $p < 0.001$). The model for estimating mTD from all cases with cpRNFLT alone is: mTD = -36.4 + 0.367 × cpRNFLT (SE = 0.0426, $p < 0.001$). The model for estimating mTD from all cases with cpVD alone is: mTD = -94.3 + 1.65 × cpVD (SE = 0.180, $p < 0.001$). cpRNFLT: circumpapillary retinal nerve fiber layer thickness; cpVD: circumpapillary vessel density; SE: standard error


Potentially eligible eyes, n= 266
Excluded eyes, n= 112
Eligible eyes, n= 154
The eye not selected if both eyes of the subject are eligible, n= 42
Included eyes, n= 112

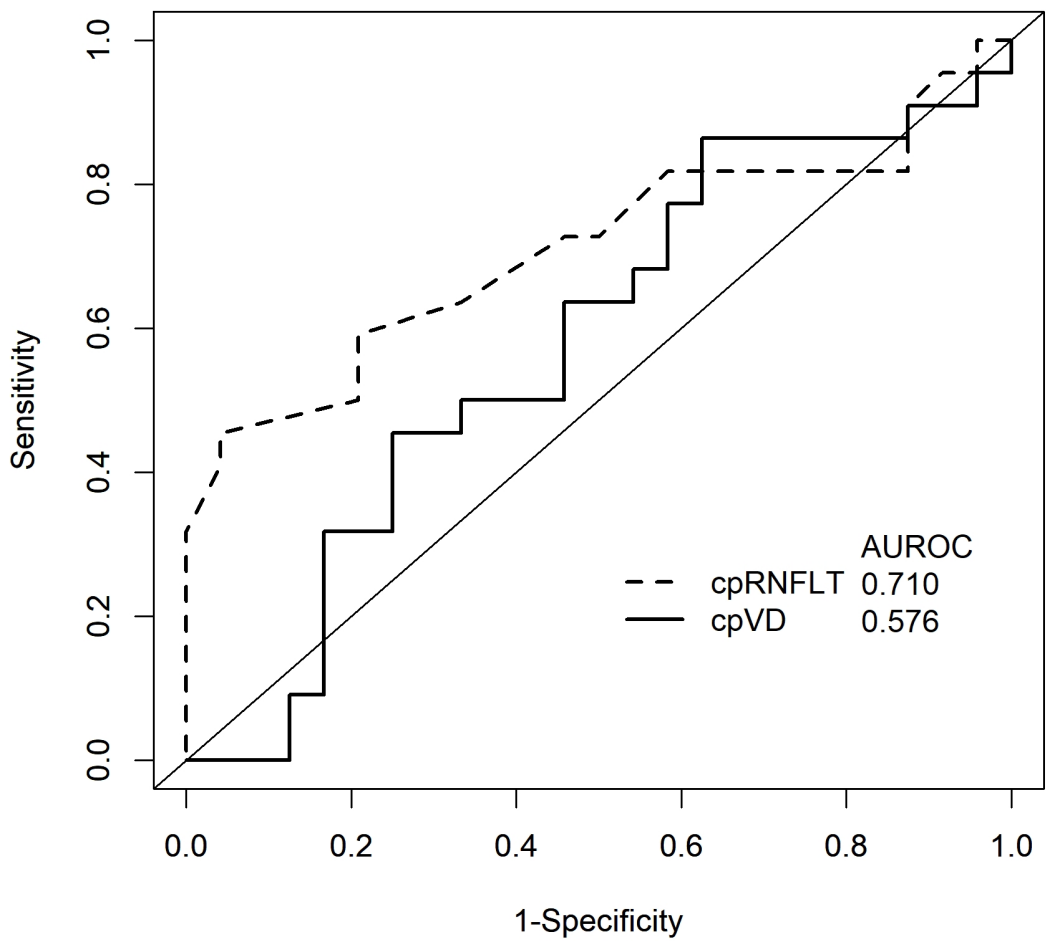
A


normal vs glaucoma
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUROC
cpRNFLT 0.969
cpVD 0.872

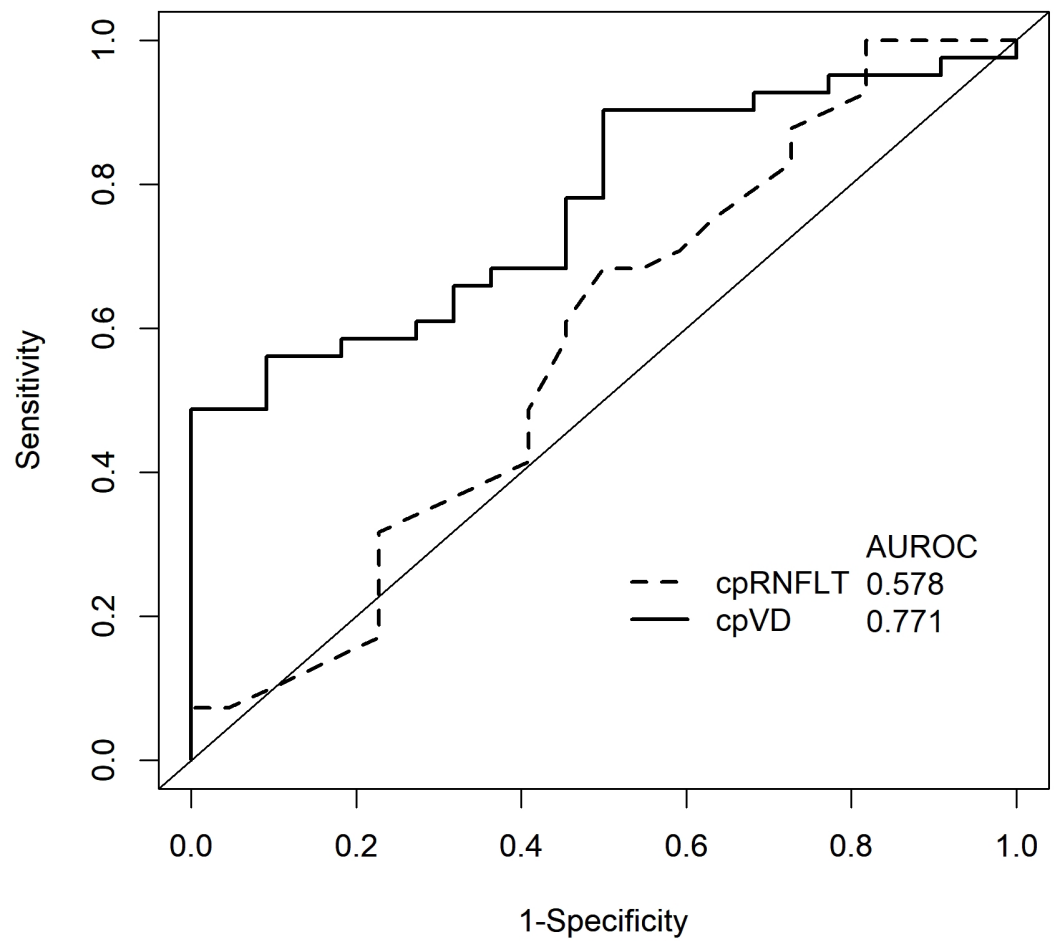
B

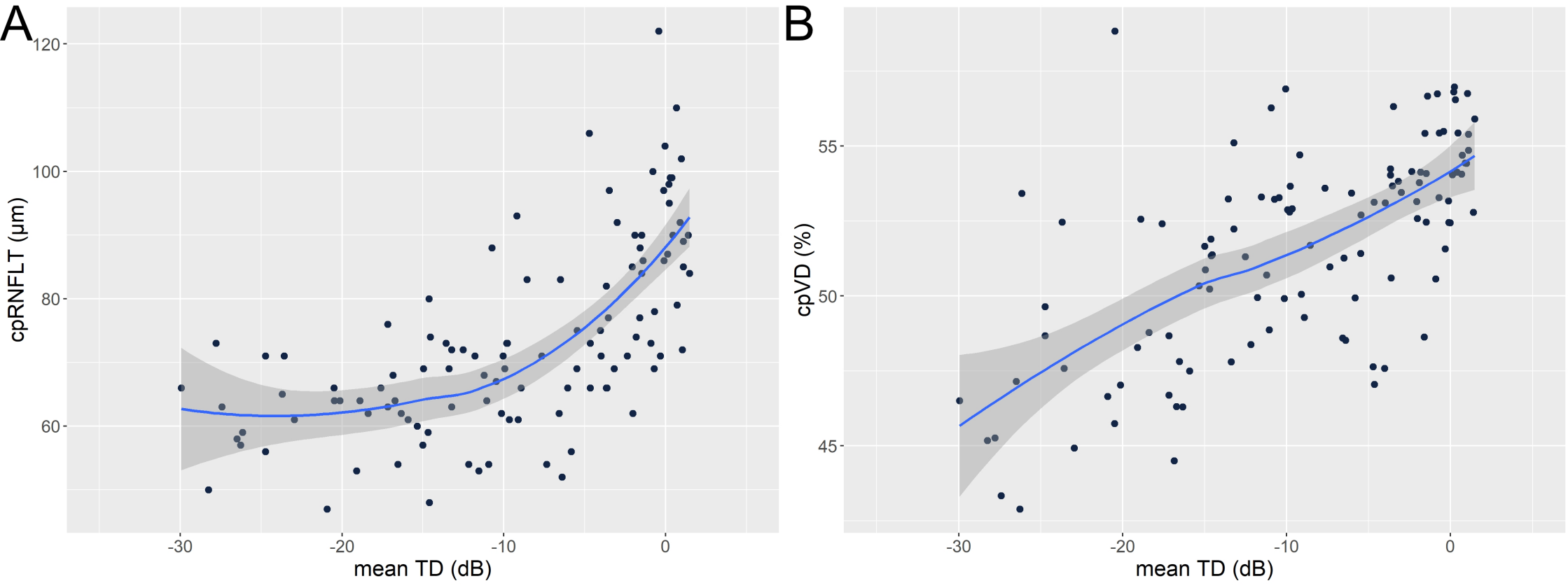

normal vs early
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUROC
cpRNFLT 0.929
cpVD 0.783

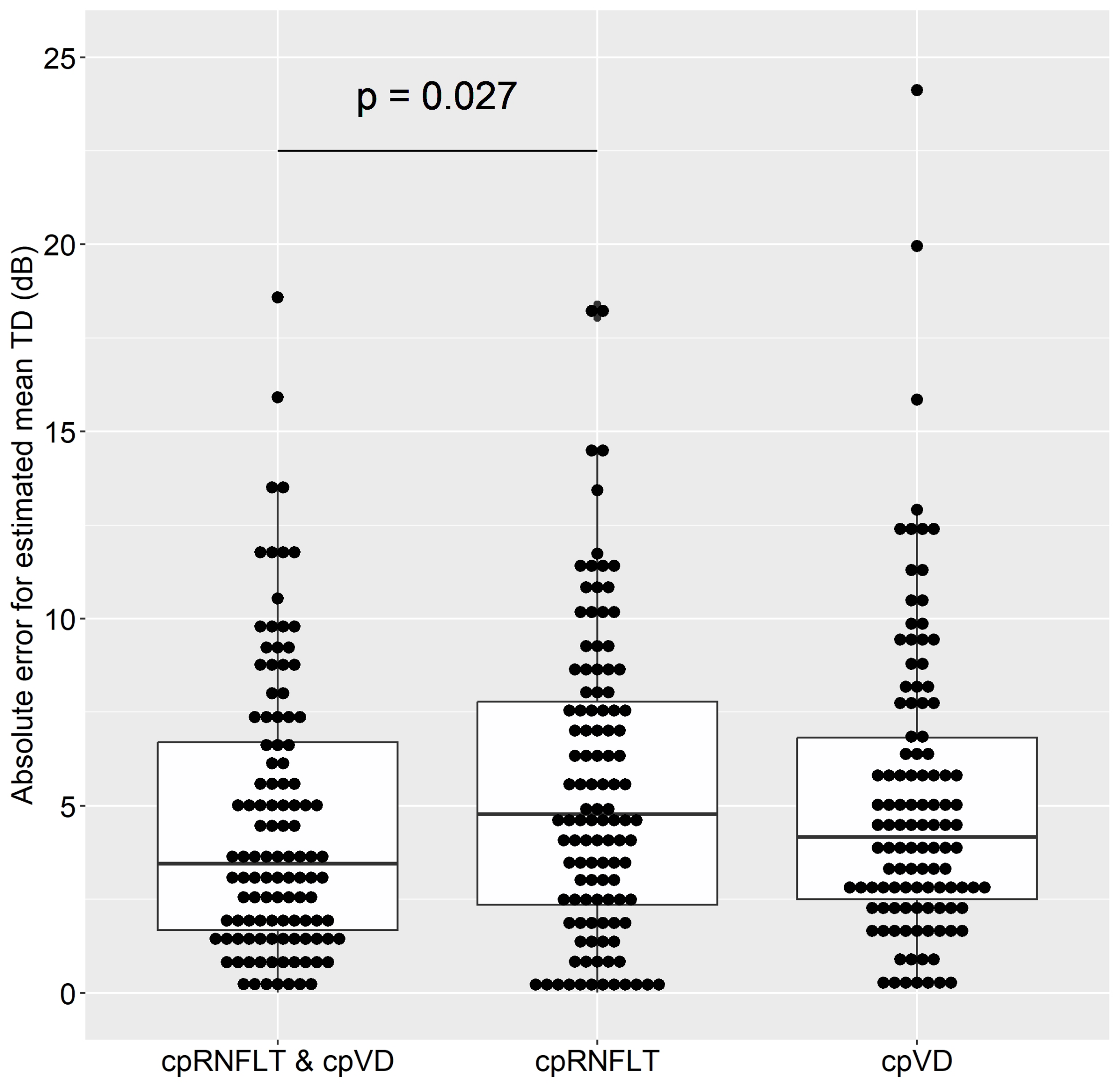
C


early vs moderate
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUROC
cpRNFLT 0.710
cpVD 0.576

D


moderate vs severe
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUROC
cpRNFLT 0.578
cpVD 0.771


A
120
100
80
60
cpRNFLT (µm)
-30
-20
-10
0
mean TD (dB)
B
55
50
45
cpVD (%)
-30
-20
-10
0
mean TD (dB)


p = 0.027
Absolute error for estimated mean TD (dB)
25
20
15
10
5
0
cpRNFLT & cpVD
cpRNFLT
cpVD