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ORIGINAL ARTICLE

Retinal Neural Layer Thickness and Contrast Sensitivity in Type 2 Diabetes Without Clinical Retinopathy: A Cross-Sectional Study

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ABSTRACT

Background: Retinal neural dysfunction may occur in type 2 diabetes mellitus (T2DM) before clinically visible diabetic retinopathy.

Objective: We evaluated whether retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCL-IPL) thickness were associated with contrast sensitivity in adults with T2DM without clinical retinopathy.

Methods: This cross-sectional study included 30 eyes from 16 participants examined from September 2024 to June 2025. Swept-source optical coherence tomography measured average and quadrant RNFL thickness and macular GCL-IPL thickness. Monocular contrast sensitivity was assessed with the Pelli-Robson chart. Source-reported analyses included exploratory Spearman correlations, generalized estimating equations (GEE) for inter-eye clustering, and exploratory receiver operating characteristic (ROC) analysis.

Results: Mean RNFL thickness was 101.3 ± 12.55 µm, GCL-IPL thickness was 81.53 ± 7.34 µm, and contrast sensitivity was 1.773 ± 0.227 logCS. Eye-level correlations with contrast sensitivity were ρ=0.758 for GCL-IPL and ρ=0.640 for average RNFL (both source-reported p<0.001). In the exploratory GEE model, coefficients were 0.0104 logCS per µm for GCL-IPL (95% CI 0.001-0.019) and 0.0062 for RNFL (95% CI 0.001-0.011). Exploratory AUCs were 0.872 and 0.804, respectively.

Conclusion: Thicker GCL-IPL and RNFL measurements were associated with better contrast sensitivity in this small cohort. The estimates are hypothesis-generating and require confirmation with participant-level data, larger samples, and external validation before clinical use.

1. Introduction

Diabetic retinopathy (DR) remains a major cause of preventable visual impairment, and its global burden is projected to rise substantially through 2045[1]. Conventional screening appropriately centers on clinically detectable microvascular lesions, including microaneurysms, hemorrhages, and macular edema. However, a lesion-based framework may not capture the earliest functional or neural consequences of diabetes in the retina.

The retina is a neurovascular tissue in which neurons, glia, and microvessels operate as an integrated unit. Recent human studies have identified associations among retinal neural thickness, visual function, glycemic exposure, kidney involvement, and microvascular perfusion before or during the earliest clinically visible stages of DR. Cross-sectional and longitudinal findings indicate that functional change and thinning of the retinal nerve fiber layer (RNFL) or ganglion cell-inner plexiform layer (GCL-IPL) may occur in parallel with, or sometimes before, ophthalmoscopically evident vascular disease[2–9].

Optical coherence tomography (OCT) permits noninvasive, reproducible quantification of these neural compartments. The peripapillary retinal nerve fiber layer (RNFL) represents retinal ganglion cell axons, whereas the macular ganglion cell-inner plexiform layer (GCL-IPL) captures ganglion cell bodies and dendritic/synaptic tissue. Adaptive-optics, swept-source OCT, and OCT angiography studies have shown that neural-layer measurements and vascular metrics may provide complementary rather than interchangeable information. Their results vary by diabetes type, OCT platform, retinal region, systemic phenotype, and comparator group, cautioning against treating one thickness value as a universal biomarker[10–17].

High-contrast visual acuity can remain normal despite difficulties in low-contrast or real-world visual tasks. Contrast sensitivity measures the ability to distinguish small luminance differences and therefore complements standard acuity. Contemporary multimodal studies using perimetry, electrophysiology, OCT, and OCT angiography have demonstrated subclinical structure-function abnormalities in prediabetes and diabetes, while also showing that neural, vascular, systemic, and cognitive phenotypes can modify the observed signal[18–23]. The Pelli-Robson chart provides a practical letter-based estimate of contrast sensitivity for clinical research.

Recent cohorts have further characterized macular neural and microvascular alterations, the influence of glycemic control and systemic hypertension, central-peripheral retinal patterns, OCT-contrast-sensitivity relationships, diabetes phenotypes, and longitudinal change in eyes without DR[24–32]. Nevertheless, few studies have evaluated peripapillary RNFL, macular GCL-IPL, and Pelli-Robson contrast sensitivity together while accounting for correlation between fellow eyes. Evidence from Indonesian clinical populations remains limited, and the relative contributions of average RNFL, quadrant RNFL, and GCL-IPL to contrast sensitivity are uncertain.

Structural thickness and visual performance are not interchangeable constructs. OCT provides an anatomical measurement generated by device- and algorithm-specific segmentation, whereas contrast sensitivity is a psychophysical response that also depends on refraction, ocular media, attention, chart luminance, and test familiarity. A cross-sectional association between them may reflect a shared retinal process, but it may also be influenced by age, glycemic exposure, axial and optical characteristics, or unmeasured systemic factors. A useful study must therefore report both the magnitude of association and the constraints on its interpretation rather than converting a correlation directly into a diagnostic claim.

The use of two eyes creates an additional design issue. Fellow eyes share genetic, metabolic, and environmental exposures, so their measurements are usually more similar than observations from two unrelated people. Treating every eye as independent can narrow uncertainty and inflate apparent statistical evidence. Ophthalmic studies may select one eye, average both eyes, or use a model that represents within-person correlation; the choice must match the estimand and available sample size. In a small cohort, even a nominally appropriate clustered model requires restraint because robust variance estimation relies on having enough independent participant clusters.

Diagnostic-performance analysis raises a separate concern. ROC curves describe ranking within the observed sample and do not establish that a cutoff will transport to a different clinic, OCT device, or case mix. Selecting the cutoff that maximizes the Youden index and then reporting its performance on the same observations creates optimism, particularly when the outcome group is small. ROC results from the present dataset can therefore only indicate whether future validation may be worthwhile. They cannot define a clinical threshold or replace established examinations for diabetic retinopathy.

The novelty of this study lies in its integrated evaluation of two complementary inner-retinal structural measures—peripapillary RNFL and macular GCL-IPL thickness—together with monocular Pelli-Robson contrast sensitivity in an Indonesian cohort with T2DM but no clinically detectable DR. Rather than treating OCT thickness as a stand-alone diagnostic marker, the study places anatomical and psychophysical measurements within a single exploratory structure-function framework, explicitly acknowledges the dependence between fellow eyes, and distinguishes association estimation from diagnostic validation. This combination addresses a locally underrepresented population and a stage of disease at which conventional fundus examination may still appear normal, while preserving the uncertainty created by a modest number of independent participants. Accordingly, the primary aim of this study was to estimate the associations of average RNFL and GCL-IPL thickness with contrast sensitivity in adults with T2DM without clinical DR. The secondary, explicitly exploratory aims were to describe quadrant-specific RNFL relationships, evaluate an adjusted model that accounts for measurements from both eyes, and characterize sample-specific ROC performance without proposing clinical thresholds. The study design and intended exploratory structure-function pathway are detailed conceptually in Figure 1.

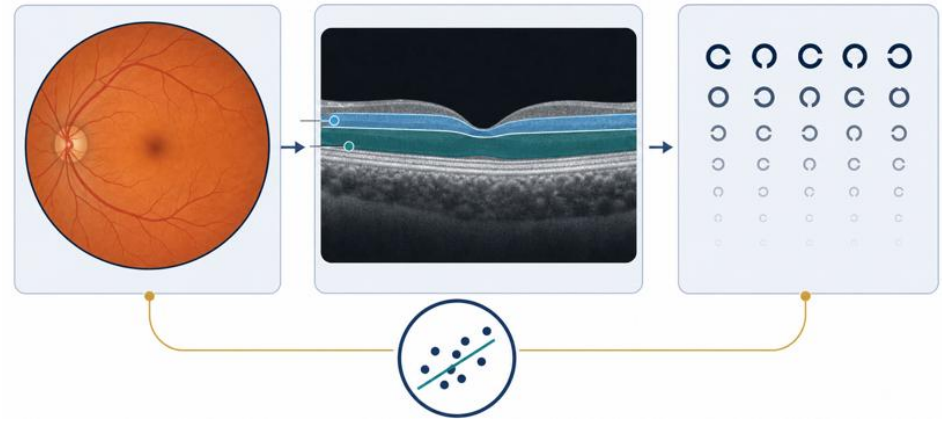

Figure 1. Conceptual graphical abstract of the study framework. Adults with type 2 diabetes mellitus and no clinically detectable diabetic retinopathy underwent swept-source optical coherence tomography of the retinal nerve fiber layer and ganglion cell-inner plexiform layer and monocular Pelli-Robson contrast-sensitivity testing. The illustration depicts the study's exploratory structure-function framework and does not display participant data, diagnostic thresholds, or causal effects. Created as a conceptual illustration for this manuscript.

2. Methods

Study design, setting, and reporting

This cross-sectional observational study was conducted in the Department of Ophthalmology, RSUP Dr. Mohammad Hoesin, Palembang, Indonesia, from September 2024 through June 2025. Reporting followed the STROBE recommendations for cross-sectional studies[33]. The study evaluated retinal structure and visual function at a single assessment period; it was not designed to establish temporal sequence, causality, progression, or treatment effects.

The Institutional Review Board of RSUP Dr. Mohammad Hoesin approved the study (Reference Number: 08.42-06/2024). Procedures were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent after receiving information about the examinations, foreseeable risks, and their rights. The source document did not provide a verifiable trial-registry identifier; because registration is not intrinsic to this non-interventional cross-sectional design, no registration claim is made here.

Participants and eligibility

Adults with an established clinical diagnosis of T2DM were recruited from diabetes and ophthalmology outpatient services. The source protocol specified an intended age range of 30-60 years, whereas the aggregate results included an observed maximum age of 62 years; this eligibility discrepancy requires confirmation against the participant-level screening record before submission. Eligibility otherwise required absence of clinical DR on dilated fundus examination and stereoscopic photographic assessment, adequate media clarity for OCT and contrast-sensitivity testing, and willingness to complete the study procedures. HbA_{1c} was treated as a contemporaneous metabolic characteristic rather than an eligibility threshold, because the observed range included values below the diagnostic cutoff in people with established, treated diabetes.

Exclusion criteria were corneal opacity or substantial astigmatism that impaired image or chart quality; cataract judged sufficient to interfere with testing; glaucoma, ocular hypertension above 21 mmHg, or other optic neuropathy; high myopia of 6 diopters or more; retinal detachment or other retinal disease; prior ocular surgery other than uncomplicated cataract surgery; and medication or systemic conditions judged likely to materially affect contrast sensitivity or retinal structure. Both eyes were eligible when they independently met ocular criteria.

The source protocol anticipated 25 independent participants for detecting a correlation of approximately 0.60 with 80% power at a two-sided alpha of 0.05. The available analysis included 16 participants contributing 30 eyes. Because two eyes from one participant do not provide the same information as two independent participants, the planned independent-participant target was not achieved. The present analyses are therefore described as exploratory, and no post-hoc power calculation was used to claim adequacy.

Clinical and ophthalmic examination

A trained clinical team recorded age, sex, diabetes duration, and the most recent HbA_{1c} measured within three months of the ophthalmic visit. Best-corrected visual acuity (BCVA) was measured with an Early Treatment Diabetic Retinopathy Study chart at four meters and converted to logarithm of the minimum angle of resolution (logMAR). Intraocular pressure was measured by Goldmann applanation tonometry; the mean of three measurements was recorded. Slit-lamp biomicroscopy assessed the anterior segment and lens. After pharmacologic dilation with topical tropicamide 1% and phenylephrine 2.5%, the posterior segment was examined by an ophthalmologist using direct and indirect ophthalmoscopy. The absence of DR and other retinal pathology was confirmed from the available clinical examination and photographic assessment. Examiner masking to OCT or contrast-sensitivity results was not documented and is not assumed.

Swept-source OCT acquisition

Retinal imaging was performed with a Topcon DRI OCT Triton Plus swept-source system (Topcon Corporation, Tokyo, Japan; center wavelength approximately 1050 nm). A disc-centered cube scan was used to obtain average peripapillary RNFL thickness and the superior, inferior, nasal, and temporal quadrant measurements. A macular cube scan was used for automated GCL-IPL and central macular thickness measurements. Values were recorded in µm.

Scans were reviewed for centration, segmentation, motion artifact, and signal quality. The source protocol required a quality score of at least 6/10. Automated segmentation errors were to be corrected or the scan repeated, although the number of repeated or excluded scans was not available in the aggregate report. Device-specific normative color coding was not used as a diagnostic outcome in the present analysis.

Contrast-sensitivity measurement

Monocular letter contrast sensitivity was assessed with a printed Pelli-Robson chart at one meter with habitual distance correction updated by the study refraction. Testing was performed under standardized room illumination of approximately 85 cd/m^2 by one trained examiner. The right eye was tested first, followed by the left eye after a short rest. The stopping rule was the lowest triplet contrast at which at least two of three letters were correctly identified. Scores were expressed as log_{10} contrast sensitivity (logCS).

Contrast sensitivity was analyzed primarily as a continuous outcome. For the exploratory ROC analysis only, reduced contrast sensitivity was operationally defined in the source analysis as logCS <1.65. This sample-specific dichotomization was not treated as a

validated disease definition or a clinical decision threshold.

Statistical analysis

Participant-level characteristics were summarized across 16 people and ocular characteristics across 30 eyes. Continuous variables were reported as mean ± standard deviation and range because those were the available aggregate summaries; categorical variables were reported as counts and percentages with explicit denominators. The source analysis did not provide a missing-data table, so complete-case denominators were inferred only where the table explicitly contained 30 eyes.

Crude eye-level relationships between retinal measurements and logCS were described using Spearman rank correlations. These coefficients are useful descriptive measures, but their conventional p values treat eyes as independent and may overstate precision. The source analysis used a Bonferroni threshold of 0.007 for its primary structural correlation family. Cluster-naive Fisher-z confidence intervals were removed from the revised report because they did not account for fellow-eye dependence.

To use measurements from both eyes while accounting for within-participant correlation, the source analysis fitted a Gaussian generalized estimating equation (GEE) with an identity link, exchangeable working correlation, and robust standard errors. Average RNFL, GCL-IPL, HbA_{1c}, and age were included as predictors of continuous logCS. GEE is a recognized approach for correlated ophthalmic data; however, sandwich standard errors can perform poorly with few clusters[34]. With only 16 participants, the model was therefore interpreted as exploratory and no variable was called an independent predictor in a causal or validated prognostic sense.

Exploratory ROC curves characterized discrimination of GCL-IPL and average RNFL for the operational outcome logCS <1.65. Areas under the curve (AUCs) and 95% confidence intervals were source-reported. No bootstrap optimism correction, internal validation, calibration assessment, or external validation was available. Source-reported analyses used SPSS 24.0 and R 4.3.2 with geepack and pROC. Individual-level data and executable code were unavailable for this manuscript revision, so no statistic was independently recomputed.

Outcome definitions and analytical hierarchy

The continuous Pelli-Robson logCS score was the principal functional outcome. Average RNFL and macular GCL-IPL thickness were the principal structural exposures because they represent the two inner-retinal compartments central to the study question. Quadrant RNFL coefficients were secondary descriptors. Central macular thickness, BCVA, HbA_{1c}, diabetes duration, and age were contextual variables rather than interchangeable primary endpoints. The operational binary contrast-sensitivity variable was reserved for exploratory discrimination analysis and did not supersede the continuous outcome.

Interpretation followed a hierarchy that separated descriptive association from clustered adjustment and discrimination. Crude Spearman coefficients described monotonic eye-level patterns. The GEE model addressed correlation between fellow eyes but was not used to claim causality or validate prediction. ROC estimates described sample ranking only. This hierarchy also prevented nominal p values from secondary quadrants, subgroups, or cut-point searches from being treated as equivalent to a prespecified confirmatory primary analysis.

Effect estimates were interpreted with their units. A GEE coefficient for a retinal layer represents the mean difference in logCS associated with a one-micrometer difference in thickness, conditional on the included variables and under the fitted marginal model. The HbA_{1c} coefficient represents a cross-sectional association per percentage point, not an intervention effect. Because RNFL and GCL-IPL may be correlated, each coefficient also depends on simultaneous inclusion of the other layer; without raw-data diagnostics, collinearity and influence could not be quantified.

Bias, precision, and sensitivity considerations

Selection bias was possible because recruitment occurred in tertiary outpatient services and the number of people screened, excluded, or declining participation was not available. Restricting the sample to eyes with adequate media and image quality improves measurement feasibility but may omit patients with more complex ocular disease. The analysis therefore estimates associations among the observed eligible participants and should not be interpreted as a prevalence estimate for all people with T2DM in South Sumatra or Indonesia.

Information bias could arise from psychophysical test variability, unrecorded examiner masking, segmentation error, and use of the right-eye-first testing sequence. Standardized distance, lighting, refraction, a common examiner, and scan-quality review were intended to reduce measurement variation. Nevertheless, repeatability coefficients, duplicate grading, axial length, pupil diameter, exact lens status, and device export files were not available. These unmeasured features could contribute to both random error and systematic differences.

Precision was primarily constrained by the 16 independent participants. A participant-level analysis using one randomly selected eye, the mean of both eyes, or a bootstrap resampled by participant would have been informative sensitivity analyses, as would a parsimonious mixed-effects model. They were not reconstructed from aggregate tables. The report therefore preserves source estimates, identifies their analytical assumptions, and avoids presenting absent sensitivity analyses as performed.

3. Results

Participant and ocular characteristics

Sixteen participants contributed 30 eligible eyes. Two participants therefore contributed one eye and 14 contributed both eyes. Reasons for excluding the fellow eyes were not available in the aggregate report. Mean participant age was 52.94 ± 8.39 years (range 38-62), and 10 of 16 participants (62.5%) were women. Mean HbA_{1c} was 7.19 ± 1.24%, and mean known diabetes duration was 3.00 ± 2.13 years. The complete participant-level demographic and clinical profile is detailed in Table 1.

At the eye level, mean BCVA was 0.04 ± 0.08 logMAR and mean Pelli-Robson contrast sensitivity was 1.773 ± 0.227 logCS. Twelve of 30 eyes (40.0%) met the source-defined exploratory criterion of logCS <1.65. Mean average RNFL thickness was 101.3 ± 12.55 µm, mean GCL-IPL thickness was 81.53 ± 7.34 µm, and mean central macular thickness was 265.8 ± 19.4 µm. All eye-level measurements and observed ranges are detailed in Table 2.

Table 1. Participant-level demographic and clinical characteristics (n=16).

Characteristic	Value
Age, years	52.94 ± 8.39 (38-62)
Female sex, n (%)	10 (62.5)
HbA1c, %	7.19 ± 1.24 (5.8-9.2)
Known diabetes duration, years	3.00 ± 2.13 (0.5-9.0)

Values are mean ± standard deviation (range) unless otherwise indicated. HbA_{1c}, glycated hemoglobin.

Table 2. Eye-level ophthalmic measurements (30 eyes from 16 participants).

Measurement	Mean ± SD or n (%)	Range
Intraocular pressure, mmHg	15.12 ± 3.21	10-21
BCVA, logMAR	0.04 ± 0.08	0-0.20
Contrast sensitivity, logCS	1.773 ± 0.227	1.30-2.00
Eyes with logCS <1.65, n (%)	12 (40.0)	-
Average RNFL, µm	101.3 ± 12.55	74-126
Superior RNFL, µm	98.2 ± 14.3	72-131
Inferior RNFL, µm	113.9 ± 16.2	89-147
Nasal RNFL, µm	85.6 ± 11.8	61-112
Temporal RNFL, µm	92.3 ± 13.5	68-122
GCL-IPL, µm	81.53 ± 7.34	67-93
Central macular thickness, µm	265.8 ± 19.4	237-301

Notes: BCVA, best-corrected visual acuity; GCL-IPL, ganglion cell-inner plexiform layer; logCS, log_{10} contrast sensitivity; logMAR, logarithm of the minimum angle of resolution; RNFL, retinal nerve fiber layer; SD, standard deviation.

Exploratory eye-level correlations

The source-reported crude eye-level Spearman coefficient between GCL-IPL thickness and contrast sensitivity was 0.758 (p<0.001), and the coefficient for average RNFL thickness was 0.640 (p<0.001). HbA_{1c} had an inverse crude correlation with logCS (ρ=-0.512, p=0.004), whereas BCVA, diabetes duration, and age had smaller coefficients with nominal p values above 0.05. These p values do not correct for fellow-eye clustering and are presented as exploratory descriptors. The complete numeric coefficient profile is detailed in Table 3 and displayed graphically in Figure 2A.

Among RNFL quadrants, the source-reported eye-level coefficients were 0.612 for the inferior quadrant, 0.583 for the superior quadrant, 0.341 for the nasal quadrant, and 0.288 for the temporal quadrant. The descriptive pattern suggests that superior and inferior arcuate measurements may carry more structure-function information in this sample, but formal comparison between dependent correlation coefficients was not reported.

Table 3. Source-reported exploratory eye-level Spearman correlations with contrast sensitivity.

Measure	Spearman ρ	Nominal p value
GCL-IPL thickness	0.758	<0.001
Average RNFL thickness	0.640	<0.001
Superior RNFL thickness	0.583	<0.001
Inferior RNFL thickness	0.612	<0.001
Nasal RNFL thickness	0.341	0.063
Temporal RNFL thickness	0.288	0.112
HbA1c	-0.512	0.004
Diabetes duration	-0.265	0.147
Age	-0.098	0.569
BCVA	-0.182	0.283

These crude coefficients and p values treat eyes as independent and may overstate precision. The source analysis specified a Bonferroni threshold of 0.007 for the primary structural correlation family. BCVA, best-corrected visual acuity; GCL-IPL, ganglion cell-inner plexiform layer; HbA_{1c}, glycated hemoglobin; RNFL, retinal nerve fiber layer.

Exploratory clustering-adjusted model

In the source-reported GEE model, the coefficient for GCL-IPL thickness was 0.0104 logCS per µm (95% CI 0.001-0.019; p=0.036), and the coefficient for average RNFL was 0.0062 logCS per µm (95% CI 0.001-0.011; p=0.019). HbA_{1c} had a coefficient of -0.0876 logCS per percentage point (95% CI -0.154 to -0.021; p=0.013), whereas age had little estimated association. The full adjusted coefficient set is detailed in Table 4. Given only 16 clusters and four predictors, these estimates should be viewed as unstable exploratory adjustments rather than confirmatory independent effects.

Table 4. Source-reported exploratory generalized estimating equation for continuous contrast sensitivity.

Predictor	B (logCS per unit)	95% CI	p value
GCL-IPL, per µm	0.0104	0.001 to 0.019	0.036
Average RNFL, per µm	0.0062	0.001 to 0.011	0.019
HbA1c, per 1%	-0.0876	-0.154 to -0.021	0.013
Age, per year	-0.0012	-0.008 to 0.005	0.695

Exchangeable working correlation with source-reported robust standard errors. Estimates are exploratory because only 16 participant clusters supported four predictors. B, regression coefficient; CI, confidence interval; GCL-IPL, ganglion cell-inner plexiform layer; HbA_{1c}, glycated hemoglobin; logCS, log_{10} contrast sensitivity; RNFL, retinal nerve fiber layer.

Exploratory ROC analysis

For distinguishing the 12 eyes with logCS <1.65 from the 18 eyes at or above 1.65, the source-reported AUC was 0.872 (95% CI 0.742-1.000) for GCL-IPL thickness and 0.804 (95% CI 0.656-0.951) for average RNFL thickness. These AUC estimates are detailed in Table 5 and displayed with their source-reported 95% confidence intervals in Figure 2B. Because performance was estimated in the same small set of correlated eyes, no clinical diagnostic claim, cutoff, or screening recommendation is made.

Table 5. Source-reported exploratory discrimination for logCS <1.65.

Measure	AUC	95% CI
GCL-IPL thickness	0.872	0.742-1.000
Average RNFL thickness	0.804	0.656-0.951

AUC estimates and confidence intervals were source-reported from the same small sample and were not internally or externally validated. AUC, area under the receiver operating characteristic curve; CI, confidence interval; GCL-IPL, ganglion cell-inner plexiform layer; logCS, log_{10} contrast sensitivity; RNFL, retinal nerve fiber layer.

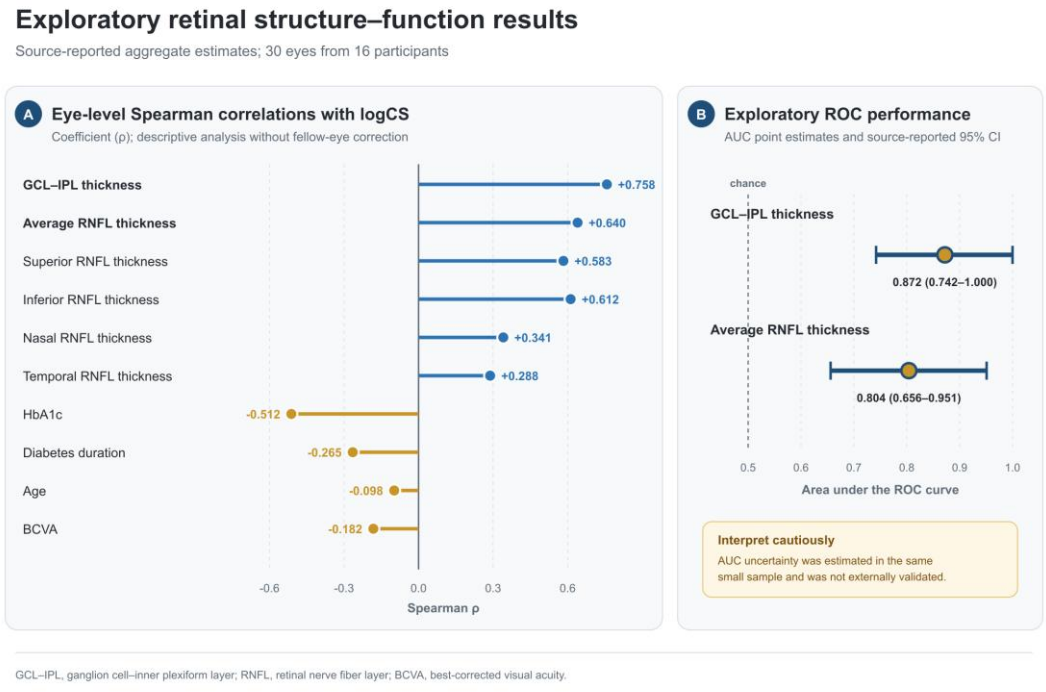

Figure 2. Source-reported exploratory retinal structure-function results. Panel A displays source-reported Spearman coefficients for retinal structural and clinical measures with logCS among 30 eyes from 16 participants. These descriptive coefficients do not account for fellow-eye dependence. Panel B displays source-reported AUC estimates and 95% confidence intervals for GCL-IPL and average RNFL thickness in distinguishing eyes with logCS <1.65. Performance was estimated in the same small sample and was not internally or externally validated. AUC, area under the receiver operating characteristic curve; BCVA, best-corrected visual acuity; CI, confidence interval; GCL-IPL, ganglion cell-inner plexiform layer; logCS, log10 contrast sensitivity; RNFL, retinal nerve fiber layer.

Distributional and data-completeness context

Observed ranges were 1.30-2.00 logCS for contrast sensitivity, 74-126 µm for average RNFL, and 67-93 µm for GCL-IPL. Quadrant RNFL means ranged from 85.6 µm nasally to 113.9 µm inferiorly. Intraocular pressure ranged from 10 to 21 mmHg, and BCVA ranged from 0 to 0.20 logMAR. These ranges describe the analyzed eyes; no distributional plots or participant-level outlier diagnostics were available to determine whether a small number of observations drove the associations.

The aggregate report contained outcome values for 30 eyes in the principal tables, but it did not provide a variable-by-variable missingness matrix. The two unobserved fellow eyes and any examinations that failed eligibility or scan-quality review could therefore not be placed in a complete recruitment flow diagram. Results use the denominators explicitly recoverable from the source tables and do not impute unreported observations.

For scale, the fitted GEE coefficients correspond to estimated differences of 0.104 logCS per 10-micrometer difference in GCL-IPL and 0.062 logCS per 10-micrometer difference in average RNFL, holding the other modeled variables constant. These arithmetic rescalings aid interpretation but do not increase precision. The simultaneous inclusion of two retinal layers and low cluster-to-parameter ratio preclude ranking them as validated independent effects.

The upper confidence limit for the GCL-IPL AUC reached 1.000, a pattern compatible with sparse outcome data rather than evidence of near-perfect transportable discrimination. The source-defined logCS boundary and absence of internal or external validation limit interpretation. Predictive values would also vary with the prevalence of reduced contrast sensitivity in a target population and are therefore not used to support clinical implementation.

4. Discussion

Principal interpretation

This exploratory cross-sectional study found that thicker macular GCL-IPL and average peripapillary RNFL measurements were associated with better Pelli-Robson contrast sensitivity in adults with T2DM and no clinically detectable DR. The crude eye-level association was numerically larger for GCL-IPL than for average RNFL, and both remained positive in the source-reported clustering-adjusted model. Inferior and superior RNFL quadrants showed the largest crude coefficients among quadrants. These findings support a structure-function signal in the inner retina, but they do not demonstrate that OCT thinning causes contrast loss, precedes it in these participants, or can diagnose an early retinal disease state. The coefficients are detailed in Tables 3 and 4, while the ordered profile in Figure 2A makes the descriptive pattern visible, including the negative HbA_{1c} association and smaller clinical coefficients.

The revised interpretation differs materially from a predictive framing. In a sample of 16 participants, a high correlation or AUC can arise from sampling variation, shared measurement factors, influential observations, or duplicated participant-level exposures across both eyes. The analysis is therefore most informative as an estimate-generating study: it identifies GCL-IPL and RNFL as plausible candidate structural measures for a larger, prospectively designed structure-function investigation. Likewise, the overlapping uncertainty intervals detailed in Table 5 and Figure 2B do not support ranking either retinal layer as a validated discriminator.

The three analytical views answer different questions and should be read together. Table 3 describes the unadjusted ordering of eye-level associations but does not correct its nominal p values for the dependence between fellow eyes. Table 4 applies a marginal model to that dependence, yet four coefficients are estimated from only 16 independent participant clusters. Table 5 and Figure 2B then describe ranking for a sample-defined binary outcome without validation. Agreement in direction across these views strengthens the rationale for replication, but it cannot overcome their shared dependence on the same small cross-sectional sample. This distinction prevents a visually strong coefficient or AUC from being interpreted as evidence of temporal prediction or clinical utility.

Relation to previous structural-functional evidence

The direction of the findings is consistent with recent cross-sectional and longitudinal evidence showing that neural-layer measurements, microvascular perfusion, and retinal function can change before or during the earliest clinical stage of DR[2–9,13–17,20,23,24,32]. These studies provide a biologically and clinically credible context for the positive GCL-IPL and RNFL coefficients observed here, while also demonstrating that neural and vascular findings are heterogeneous.

The strongest recent comparisons use multimodal or longitudinal designs, including swept-source OCT and OCT angiography, to distinguish neural-layer change from coexisting vascular alteration[8,20,23–27,30–32]. However, not every cohort identifies GCL-IPL thinning at the same stage, and layer estimates vary with segmentation, scan geometry, systemic phenotype, and comparator selection. The current study has no non-diabetic comparator and therefore cannot determine whether mean thickness was lower than expected for age or device.

The functional findings align with contemporary studies showing that high-contrast acuity, contrast sensitivity, perimetry, and electrophysiology capture different dimensions of retinal function[2,5,6,18,22,28]. In the present cohort, mean BCVA was close to 0 logMAR while contrast scores varied widely enough to reveal structural associations. This supports contrast sensitivity as a complementary research outcome, not as a stand-alone clinical screening test.

Within that literature, the contribution of the present study is deliberately specific. It does not claim to establish retinal neurodegeneration as a new concept. Instead, it evaluates whether two complementary neural compartments and a clinically feasible contrast measure vary together in an Indonesian cohort whose fundus examinations showed no clinical DR. The simultaneous assessment of average and quadrant RNFL, macular GCL-IPL, and monocular Pelli-Robson performance creates a coherent structure-function hypothesis for a future participant-powered study. Its value therefore lies in the integrated measurement framework and the locally underrepresented setting, not in asserting a universal threshold or a population prevalence estimate.

Potential biological interpretation

Retinal ganglion cells and their axons have high metabolic demand and depend on coordinated support from Müller cells, astrocytes, microglia, capillary endothelium, and pericytes. Chronic hyperglycemia can disrupt this neurovascular unit through oxidative stress, altered glutamate metabolism, reduced neurotrophic support, mitochondrial dysfunction, inflammation, and impaired autoregulation. Human multimodal studies support coexistence of neural and vascular abnormalities in early diabetes[3,4,8,14,16,21,24,32]. GCL-IPL thickness integrates ganglion cell bodies and inner plexiform synaptic tissue near the macula, where structure is relevant to central visual processing. A positive association between GCL-IPL thickness and contrast sensitivity is therefore biologically plausible.

The RNFL association is also plausible because the RNFL contains ganglion cell axons that transmit retinal output. The numerically stronger superior and inferior quadrant coefficients could reflect the larger dynamic range of arcuate bundles, regional susceptibility, or simple sampling variation. The source manuscript proposed magnocellular selectivity as an explanation, but the present measurements do not isolate magnocellular pathways and Pelli-Robson scores do not identify the cellular origin of dysfunction. Mechanistic attribution should therefore remain tentative.

HbA_{1c} showed an inverse association with contrast sensitivity in the crude and adjusted source analyses. This pattern is compatible with a metabolic contribution, but HbA_{1c} was measured once within a three-month window and cannot represent long-term glycemic exposure or metabolic memory. The study lacked blood pressure, renal function, lipid levels, smoking, neuropathy status, and other potential confounders. The data therefore do not establish that improving HbA_{1c} would reverse or prevent the observed functional pattern.

Clinical and research implications

The findings do not justify adding an OCT cutoff to routine diabetes screening. The exploratory AUC estimates in Table 5 were derived from the same 30-eye sample used to evaluate performance. Such apparent discrimination is typically optimistic without resampling, independent validation, and device-specific calibration. Thickness values also depend on OCT hardware, segmentation software, scan geometry, axial length, age, and population characteristics. A universal threshold cannot be inferred.

A more defensible near-term implication is methodological. Future diabetic retinal neurodegeneration studies should combine structural OCT with functional outcomes beyond high-contrast acuity, specify the unit of analysis, and handle both eyes appropriately. They should prespecify the primary layer, primary functional endpoint, confounder set, and multiplicity strategy. If both eyes are included, sample-size calculations and analysis should be participant-aware from the outset rather than converting a participant requirement into an eye count.

A larger multicenter study could evaluate whether GCL-IPL adds information beyond age, diabetes duration, HbA_{1c} history, axial length, lens status, blood pressure, and microvascular OCT angiography metrics. Repeated OCT and contrast-sensitivity testing would allow estimation of within-person change and temporal ordering. External validation across OCT platforms and Indonesian regions would be necessary before any screening or risk-stratification application.

Strengths and limitations

Strengths include the focused phenotype of T2DM without clinical DR, use of swept-source OCT, measurement of both RNFL and GCL-IPL, monocular Pelli-Robson testing, and an attempt to account for fellow-eye clustering. Reporting the negative or weak associations for BCVA, age, and diabetes duration helps avoid selective emphasis on only the largest coefficients. The study also adds data from an Indonesian tertiary-care population that is underrepresented in the published structure-function literature.

The principal limitation is the small number of independent participants. Sixteen clusters are insufficient for stable multivariable GEE inference with four predictors, and conventional robust standard errors may be downward biased. The planned participant target was not achieved. The crude Spearman p values treat 30 eyes as independent and thus should not be interpreted as confirmatory. No raw data were available during revision to fit a small-sample-corrected GEE, mixed-effects model, participant-level sensitivity analysis, or bootstrap confidence intervals.

Additional limitations include cross-sectional design, single-center convenience recruitment, no non-diabetic comparator, restricted age range, incomplete documentation of participant flow and missingness, potential examiner non-masking, and possible residual effects of lens status or refractive error. HbA_{1c} and diabetes duration were incompletely characterized as

cumulative exposures. OCT segmentation reproducibility and intergrader reliability were not reported. The operational definition of reduced contrast sensitivity was not externally validated.

Finally, only aggregate statistical outputs were available for this analysis, preventing verification against participant-level observations, evaluation of influential clusters, and reproducible reanalysis. The reported estimates should therefore be interpreted as exploratory and verified against the original dataset and executable analysis before external use.

Integrated interpretation of the observed pattern

The ordering of the reported associations adds context. GCL-IPL had the largest crude coefficient, followed by average RNFL and the inferior and superior RNFL quadrants, whereas BCVA had a comparatively small coefficient. This pattern is compatible with an inner-retinal structure-function relationship, but it is not proof of specificity. GCL-IPL, RNFL, and contrast sensitivity may each covary with a common determinant, and the aggregate report cannot show whether the relationship is linear, monotonic throughout the range, or concentrated among a few influential eyes or participants.

Differences among studies should not be reduced to whether a p value crosses a conventional threshold. Some cohorts compare diabetes with healthy controls, whereas this study evaluates within-diabetes covariation. Some analyses use one eye, and others use both eyes with different methods for dependence. Layer boundaries, scan diameter, signal strength, refractive status, age distribution, diabetes duration, and functional instruments also differ. A stronger correlation in one small dataset does not imply a superior biomarker; transportability depends on standardized measurement and replication across these design dimensions.

The absence of visible DR should likewise be interpreted as a clinical classification, not proof that the retinal microvasculature was normal. Standard examination and photography may not detect all capillary or neurovascular abnormalities measurable with OCT angiography or other research methods. Diabetes-related neural and vascular changes can coexist and interact[3,10–17,21,24–27,31,32]. The present data support an inner-retinal association in a clinically no-DR group, but they cannot separate a purely neural process from subclinical microvascular contributions.

Measurement and anatomical considerations

GCL-IPL may show a closer numerical relationship with central contrast performance because the macular measurement samples ganglion cell bodies and synaptic layers within the region most relevant to letter recognition. Peripapillary RNFL is spatially displaced from the macula and aggregates axons originating across the retina. This anatomical explanation is plausible, but direct comparison of correlation magnitudes requires methods that account for their dependence. The study did not perform such a validated comparison, so the two layers should be treated as complementary candidates.

OCT thickness is a derived measurement rather than a direct cell count. Segmentation boundaries are set by software and can be affected by signal strength, centration, media clarity, axial length, pathology, and device updates. A one-micrometer difference does not necessarily have the same biological meaning across devices or regions. The present results apply to the Topcon swept-source acquisition and processing described in Methods. Device-specific repeatability and between-device agreement should be quantified before comparing a proposed threshold across clinical platforms[11,12,15,24,30].

Contrast sensitivity is also a composite behavioral endpoint. Pelli-Robson testing emphasizes letter recognition at a relatively fixed spatial scale and does not map a complete contrast-sensitivity function. Neural adaptation, cognition, fatigue, uncorrected blur, and small variations in luminance can affect a score. The association with OCT therefore does not localize dysfunction to a single retinal cell class or visual pathway. Electrophysiology, microperimetry, color testing, and spatial-frequency-specific measures would help triangulate the functional phenotype in future work.

Implications for clinical translation

For clinical care, the immediate message is deliberately conservative. Patients with diabetes should continue to receive guideline-based retinal examinations, risk-factor management, and appropriate follow-up; an OCT neural-layer value or Pelli-Robson score from this study should not alter those pathways. An individual thickness value may fall within measurement variation or reflect anatomy unrelated to diabetes, and a value within a reference range cannot exclude functional change or future retinopathy.

A validation program should separate marker development from marker evaluation. An initial training cohort could specify quality control, candidate variables, functional outcome, and model form. Internal validation should estimate optimism and calibration, preferably by resampling participants rather than eyes. A temporally or geographically independent cohort should then evaluate discrimination, calibration, measurement repeatability, and clinical utility without reselecting the cutoff. Only after these steps would a decision-impact study be appropriate.

Sample-size planning for that work should be driven by the number of independent participants and the intended estimand. Correlation studies require allowance for within-person eye correlation and expected attrition. Multivariable models require enough participant clusters for the planned degrees of freedom, and diagnostic studies require sufficient participants with and without the target condition. Prespecified handling of missing data, nonlinear

relationships, interactions, and multiplicity would reduce the risk that attractive patterns are selected after observing a small dataset.

Methodological lessons and residual uncertainty

The limitations interact rather than operate independently. Small participant numbers make estimates more sensitive to selection and measurement error; use of both eyes increases the need for a well-behaved clustered analysis; and the absence of raw data prevents evaluation of influential clusters, functional form, residual behavior, or missingness. Consequently, consistency in direction across several inner-retinal measures is more informative than any single nominal p value, confidence interval, or cutoff. Replication is required to determine whether that pattern is robust.

Residual confounding is another major constraint. Age and HbA_{1c} were included in the GEE model, but axial length, refractive error as a continuous measure, lens status, blood pressure, kidney disease, lipids, smoking, medication use, and socioeconomic or testing factors were unavailable. Adding all of these variables to the current model would not solve the problem because the sample could not support them. A larger design should measure them prospectively and prespecify a parsimonious adjustment set based on causal reasoning rather than automated variable selection.

The HbA_{1c} association deserves the same caution. A single measurement is useful for describing recent glycemic exposure but does not capture long-term trajectories, variability, or treatment changes. The source subgroup analysis divided a very small number of correlated eyes and was removed because the interaction claim did not meet the report's stated multiplicity threshold. The remaining continuous coefficient is hypothesis-generating and should not be interpreted as evidence that glycemic control modifies the structural association.

Likewise, the quadrant results are descriptive. Superior and inferior RNFL coefficients were numerically larger than nasal and temporal coefficients, but the study did not report a valid test comparing dependent correlations. Multiple quadrant examination also increases the opportunity for chance findings. Replication with spatially aligned macular function, standardized sector definitions, and a prespecified regional hypothesis is needed before assigning anatomical selectivity.

Directions for confirmatory investigation

The next study should recruit participants rather than eyes as the sample-size unit and document the numbers screened, eligible, enrolled, examined, and analyzed. Both eyes may contribute if laterality and participant identifiers are retained and the statistical plan addresses clustering. Repeated measures would permit separation of between-person differences from within-person change and would test whether structural change precedes functional decline rather than merely accompanying it.

Measurement quality should be strengthened with masked grading where feasible, saved OCT segmentation exports, prespecified scan-quality rules, repeat scans in a subset, axial-length adjustment, and documented Pelli-Robson luminance and scoring. Including a non-diabetic comparator would address mean structural and functional differences, while a spectrum of DR severity could test whether the association changes with vascular disease. OCT angiography or electrophysiology could help distinguish overlapping neural and microvascular pathways.

Analysis should emphasize effect sizes with participant-aware uncertainty. A primary model could focus on one structural exposure and one functional endpoint, with secondary layers and quadrants controlled through a prespecified multiplicity strategy. Nonlinearity, sex or glycemic modification, and cutoff performance should be examined only with adequate sample size and independent validation. Sharing a de-identified data dictionary and reproducible code, subject to ethics restrictions, would allow numerical audit and facilitate comparison across cohorts.

A confirmatory protocol should also distinguish association, prognosis, and diagnosis. An association study asks whether structure and function vary together at a defined time; a prognostic study asks whether a baseline measurement predicts a future outcome; and a diagnostic study compares a marker against a clinically meaningful reference standard. The present design answers only the first question. Clear separation of these objectives would determine the appropriate population, time horizon, sample size, statistical model, and reporting framework for subsequent research.

Longitudinal analysis should consider measurement error and expected age-related change. Repeated OCT values can vary because of acquisition and segmentation even when biology is stable, while contrast scores can improve through learning or fluctuate with testing conditions. Estimating repeatability before estimating progression would allow observed change to be separated from noise. Models with participant- and eye-level random effects could then evaluate whether within-eye neural-layer change accompanies or precedes within-eye functional change.

Finally, clinical usefulness should be judged against an explicit alternative. A new OCT or contrast marker would need to add reliable information beyond routine examination and established systemic risk factors, lead to an actionable management decision, and improve outcomes without disproportionate cost or false-positive burden. High correlation or AUC alone does not demonstrate that value. The current findings provide a rationale for rigorous validation, not evidence that screening practice should change.

Patient-centered outcomes should be incorporated alongside laboratory performance. Contrast sensitivity may matter because it relates to vision under dim illumination, reduced contrast, or glare, yet this study did not measure reading, mobility, driving, falls, work performance, or vision-related quality of life. Future cohorts should test whether neural-layer measurements explain meaningful functional limitations after accounting for acuity and ocular media. Such evidence would clarify whether the observed statistical association represents a perceptible burden to patients and whether monitoring it offers value beyond a technically interesting imaging signal. Qualitative input from people living with diabetes could also help select functional endpoints and acceptable testing pathways.

Equity and feasibility also require attention. Access to swept-source OCT, trained graders, and controlled contrast testing may differ between tertiary centers and routine diabetes services. A marker that performs well under research conditions may have limited reach if acquisition, maintenance, or interpretation is costly. Validation in varied Indonesian settings should therefore assess missing or ungradable scans, operator training, testing time, referral consequences, and affordability. These implementation outcomes are necessary to judge whether any future structure-function strategy could complement, rather than divert resources from, proven retinal screening.

5. Conclusion

In this small cross-sectional cohort of adults with T2DM and no clinically detectable diabetic retinopathy, greater GCL-IPL and average RNFL thickness were associated with better Pelli-Robson contrast sensitivity. The results support further study of inner-retinal structure-function relationships, particularly GCL-IPL, but do not establish causality, diagnostic thresholds, or a validated screening strategy. Participant-level verification, larger independent samples, longitudinal follow-up, and external validation are required before clinical application.

Declarations

Ethics approval and informed consent

The Institutional Review Board of RSUP Dr. Mohammad Hoesin, Palembang, Indonesia approved the study (Reference Number: 08.42-06/2024). The study followed the Declaration of Helsinki. All participants provided written informed consent.

Conflict of interest

The authors declare no competing interests, financial disclosures, or proprietary interests related to the devices or methods described in this manuscript.

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Author contributions

R.A. and R.R. contributed to conceptualization. R.A., P.P., and M.A.P.O.C. contributed to methodology. M.A.P.O.C. contributed to formal analysis and visualization. R.R., P.P., and M.A.P.O.C. contributed to investigation. R.A. provided resources, supervision, and project administration. R.R. and M.A.P.O.C. contributed to data curation and drafting. R.A. and P.P. contributed to review and editing.

Data availability

The dataset is available from the corresponding author on reasonable request, subject to participant confidentiality agreements and ethics requirements.

Generative AI disclosure

The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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