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Study on the Correlation between Retinal Ganglion Cell Layer Thickness Measured by OCT and the Severity of White Matter Hyperintensities in Cerebral Small Vessel Disease

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Abstract: *Objective*: To investigate the correlation between the thickness of the retinal ganglion cell layer (GCL) measured by optical coherence tomography (OCT) and the severity of white matter hyperintensities (WMH) in cerebral small vessel disease (CSVD). *Methods*: Thirty-one patients with CSVD were selected and divided into a mild group (21 cases) and a moderate-to-severe group (10 cases) based on the severity of WMH. Additionally, 30 healthy individuals were selected as the control group. All subjects underwent 3.0T cranial MRI and OCT examinations. The severity of WMH was assessed using the Fazekas scale, and the thickness of the GCL in each quadrant, as well as the average and minimum thickness, was measured to analyze their correlation with WMH and their predictive value. *Results*: Statistically significant differences were observed among the three groups in terms of GCL thickness in the superior nasal, inferior nasal, inferior, and inferior temporal quadrants, as well as the average and minimum thickness ($P < 0.05$). The average GCL thickness showed a significant negative correlation with the Fazekas score ($P < 0.05$). Multiple linear regression analysis revealed that the average GCL thickness in the moderate-to-severe WMH group was significantly lower than that in the mild group ($P < 0.05$), and type 2 diabetes mellitus enhanced this negative correlation. The ROC curve demonstrated that after adjusting for clinical factors, the area under the curve (AUC) for predicting moderate-to-severe WMH using the average GCL thickness reached 0.83. *Conclusion*: The thickness of the GCL in patients with CSVD is negatively correlated with the severity of WMH, and the average GCL thickness has good predictive value for moderate-to-severe WMH. Meanwhile, OCT, as a non-invasive fundus imaging technique, can provide a new method for the early identification of CSVD and the assessment of white matter lesions.

Keywords: Cerebral small vessel disease; White matter hyperintensities; Retinal ganglion cell layer; Optical coherence tomography

1. Introduction

Cerebral small vessel disease (CSVD) refers to a series of clinical, imaging, and pathological syndromes caused by various etiologies affecting the small arteries and their distal branches, arterioles, capillaries, venules, and small veins in the brain. It has become a common disease that seriously endangers the health of the population [1]. White matter hyperintensities (WMHs) are important imaging indicators reflecting brain parenchymal damage in CSVD and are associated with an increased risk of dementia [2]. Studies on the pathogenesis of CSVD have shown that microvascular damage often occurs significantly earlier than brain parenchymal damage [3]. However, current clinical assessment methods for CSVD are limited. Conventional CT and MRI can only display organic lesions in the brain parenchyma, while techniques such as MR perfusion imaging, arterial spin labeling, and PET are difficult to promote routinely in clinical practice due to their high cost, complex operation, and partial invasiveness [4].

Optical coherence tomography (OCT), as an emerging retinal vascular imaging technique, has become a highly promising non-invasive screening and assessment tool for CSVD due to its advantages of being non-invasive, having high resolution, being convenient and economical, allowing for continuous tracking, and enabling three-dimensional imaging [5]. However, most existing OCT-related studies have focused on the analysis of fundus lesions and fundus vascular morphological parameters, and there is a lack of research using OCT to assess CSVD [6]. Moreover, most domestic-related studies are single-center and small-sample studies, and their conclusions still need to be verified. This study aimed to detect the thickness of the retinal ganglion cell layer (GCL) in patients with CSVD using OCT and explore its correlation with the severity of WMHs, in order to find non-invasive biomarkers for white matter lesions in CSVD and provide new methods for early screening and disease assessment.

2. Materials and methods

2.1. General information

Thirty-one patients with cerebral small vessel disease (CSVD) who were hospitalized in the neurology department of the hospital from January 2023 to June 2025 were selected. Based on the results of 3.0T cranial MRI examinations, the patients were divided into two groups according to the severity of white matter hyperintensities (WMH): a mild WMH group with 21 cases and a moderate-to-severe WMH group with 10 cases. Meanwhile, 30 healthy individuals who underwent physical examinations during the same period were selected as the healthy control group. This study was approved by the hospital's ethics committee, and all subjects signed informed consent forms.

Inclusion criteria: (1) Age between 50 and 80 years old; (2) CSVD patients met the diagnostic criteria for sporadic cerebral small vessel disease outlined in the "Chinese Expert Consensus on the Diagnosis and Treatment of Cerebral Small Vessel Disease 2021"; (3) Voluntarily participated in this study and signed an informed consent form.

Exclusion criteria: (1) Patients in the acute symptomatic phase of CSVD or non-sporadic CSVD caused by metabolic, toxic, infectious, genetic, or other factors; (2) Intracranial or extracranial arterial stenosis > 50%, or non-acute cortical/subcortical cerebral infarction with a diameter > 1.5 cm; (3) A history of intracranial hemorrhage or concurrent other neurological diseases; (4) Concurrent ocular diseases that affect fundus observation; (5) Presence of contraindications for magnetic resonance imaging or inability to undergo OCT examinations and neuropsychological scale assessments.

There were no statistically significant differences among the three groups in terms of age, gender, body mass index (BMI), history of smoking and alcohol consumption, and comorbidities ($P > 0.05$), indicating comparability (**Table 1**).

Table 1. Comparison of basic information among the three groups

Item		Healthy Control Group ($n = 30$)	Mild WMH Group ($n = 21$)	Moderate-to-Severe WMH Group($n = 10$)	P value
Age (years, mean ± SD)		57.87 ± 7.78	59.43 ± 8.39	64.30 ± 6.95	0.091
Gender [n(%)]	Male	15 (50.00)	12 (57.14)	5 (50.00)	0.869
	Female	15 (50.00)	9 (42.86)	5 (50.00)	
BMI [kg/m², M (Q_1, Q_3)]		23.70 (22.23, 25.86)	23.88 (22.09, 25.54)	24.49 (23.56, 25.56)	0.464
Smoking [n(%)]	No	26 (86.67)	17 (80.95)	9 (90.00)	0.891
	Yes	4 (13.33)	4 (19.05)	1 (10.00)	
Alcohol consumption [n(%)]	No	27 (90.00)	19 (90.48)	10 (100.00)	0.846
	Yes	3 (10.00)	2 (9.52)	0 (0.00)	
Hypertension [n(%)]	No	15 (50.00)	10 (47.62)	6 (60.00)	0.806
	Yes	15 (50.00)	11 (52.38)	4 (40.00)	
Type 2 diabetes mellitus [n(%)]	No	25 (83.33)	18 (85.71)	6 (60.00)	0.260
	Yes	5 (16.67)	3 (14.29)	4 (40.00)	

2.2. Methods

(1) Cranial MRI Examination and Imaging Assessment: A 3.0T magnetic resonance scanner from GE (USA) was used to perform cranial MRI + MRA + Flair + SWI sequence scans on all subjects. Without knowledge of the patients' clinical information and grouping, two experienced senior neurologists evaluated the MRI images with reference to the "Chinese Expert Consensus on the Diagnosis and Treatment of Cerebral Small Vessel Disease 2021." The images were required to be clear, with good contrast and no significant artifacts.

(2) OCT Examination: Subjects were prohibited from smoking and consuming alcoholic beverages for 3 hours prior to the examination, and a light diet was required for at least 1.5 hours before the examination. Visual acuity testing, automatic refraction, intraocular pressure measurement, slit-lamp examination, and fundus photography were performed first to exclude ocular diseases that affect fundus observation. Using OCT equipment, the subject's mandible was placed on the chin rest, and the forehead was pressed forward against the forehead support. The height of the chin rest was adjusted so that the lateral canthus of the subject's eye was at the level of the eye position marker line. The subject was instructed to fixate on the internal fixation light inside the equipment lens, and the scanning head was aligned with the center of the subject's pupil. It was then gradually advanced until a clear fundus image appeared on the display screen, and the fundus image was adjusted to be as clear as possible. Scans were performed in 3mm×3mm and 6mm×6mm areas centered on the macular fovea and optic disc, respectively, with 4 B-scans performed at each position. If motion artifacts were present or the image quality was poor, the scan was repeated. After completing scans on both eyes, eyes with an image quality score > 5 and a signal strength index > 40 were selected for analysis. If both eyes met the criteria, the eye with better image quality was chosen.

2.3. Observation indicators

(1) The severity of WMHs was assessed using the Fazekas scale, with scores assigned separately for periventricular and deep white matter hyperintensities (0–3 points each), resulting in a total score ranging from 0-6 points. Scores of 1–3 points indicated mild WMH, while scores of 4–6 points indicated moderate-to-severe WMH.

(2) GCL Thickness Indicators: The thickness of the GCL in the superior temporal, inferior temporal, superior nasal, inferior nasal, superior, and inferior quadrants, as well as the average and minimum thickness of the GCL.

2.4. Statistical Methods

Data analysis was performed using SPSS 26.0 and R 4.4.1 software packages. Normally distributed measurement data were expressed as mean ± standard deviation (Mean ± SD), non-normally distributed data were expressed as median (Q_1, Q_3), and count data were expressed as number of cases (percentage) [n (%)]. Comparisons of measurement data among multiple groups were performed using one-way ANOVA or Kruskal-Wallis tests, while comparisons of count data were performed using Pearson chi-square tests, continuity-corrected chi-square tests, or Fisher's exact tests. Correlation analysis was performed using Spearman's method, with $P < 0.05$ considered statistically significant.

3. Results

3.1. Comparison of GCL thickness indicators among the three groups

There were statistically significant differences among the three groups in terms of GCL thickness in the superior nasal, inferior nasal, inferior, and inferior temporal quadrants, as well as the average and minimum thickness ($P < 0.05$). There were no statistically significant differences among the three groups in terms of GCL thickness in the superior temporal and superior quadrants ($P > 0.05$) (**Table 2**).

Table 2. Comparison of GCL thickness indicators among the three groups

Item	Healthy Control Group (*n*=30)	Mild WMH Group (*n*=21)	Moderate-to-Severe WMH Group (*n*=10)	*P* value
GCL TS	81.5 (79.3, 85.0)	84.0 (82.0, 87.0)	80.5 (72.3, 84.0)	0.097
GCL S	85.5 (81.3, 89.0)	86.0 (84.0, 90.0)	80.5 (70.3, 83.8)	0.053
GCL NS	87.0 (83.3, 90.8)	87.0 (85.0, 90.0)	81.0 (76.0, 84.8)	0.027
GCL NI	83.0 (79.3, 88.3)	85.0 (83.0, 90.0)	77.0 (74.0, 82.0)	0.015
GCL I	80.5 (75.3, 85.8)	83.0 (79.0, 87.0)	73.0 (68.0, 79.0)	0.020
GCL TI	82.5 (77.3, 86.0)	85.0 (80.0, 90.0)	75.0 (70.0, 78.8)	0.016
GCL average	84.0 (79.0, 86.0)	85.0 (82.0, 90.0)	78.5 (71.5, 81.0)	0.020
GCL min	80.0 (76.0, 82.0)	83.0 (79.0, 85.0)	72.5 (67.3, 77.0)	0.003

Note: GCL: Ganglion Cell Layer; TS: Superior Temporal; S: Superior; NS: Superior Nasal; NI: Inferior Nasal; I: Inferior; TI: Inferior Temporal; average: Average Thickness; min: Minimum Thickness

3.2. Correlation between average GCL thickness and Fazekas score

Spearman's rank correlation analysis revealed a significant negative correlation between the average GCL thickness and the Fazekas score in the overall study cohort ($R = -0.299$, $P < 0.05$) (**Figure 1**).

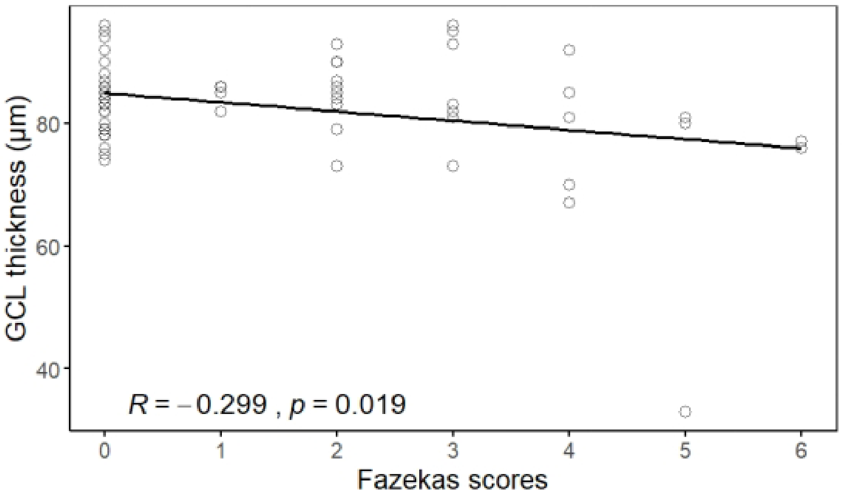


Figure 1. Spearman's rank correlation analysis between GCL thickness and Fazekas score

3.3. Regression analysis of GCL thickness and WMH severity

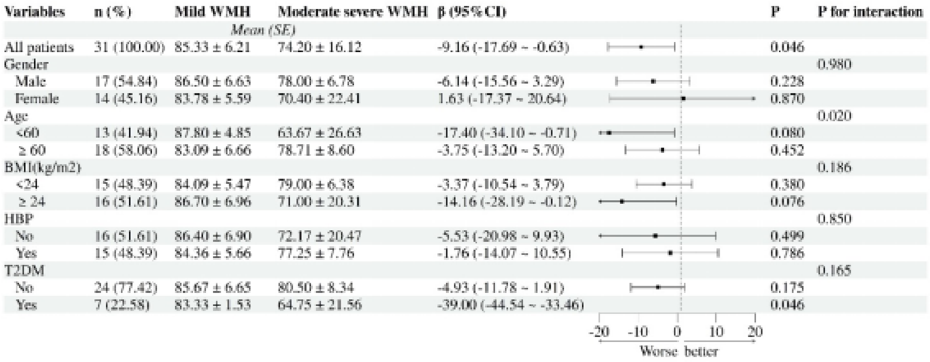
Using CSVD patients as the study subjects, a multiple linear regression model was constructed with the average GCL thickness as the dependent variable and WMH severity as the independent variable. The results showed that in the unadjusted model (Model 1), the average GCL thickness in the moderate-to-severe WMH group was lower than that in the mild WMH group (95% CI: -18.93 to -3.34, $P < 0.05$). After adjusting for age and gender (Model 2), the effect size changed slightly (95% CI: -19.62 to -3.11, $P < 0.05$). After further adjusting for hypertension and type 2 diabetes (Model 3), a significant negative correlation was observed between moderate-to-severe WMH and the average GCL thickness (95% CI: -18.17 to -0.87, $P < 0.05$) (**Table 3**).

Table 3. Linear regression analysis of WMH and GCL thickness in patients with cerebral small vessel disease

Variable	Model 1		Model 2		Model 3	
	β (95% CI)	***P***	**β (95% CI)**	***P***	**β (95% CI)**	***P***
Mild (WMH)	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Moderate-to-severe (WMH)	-11.13 (-18.93 to -3.34)	0.009	-11.36 (-19.62 to -3.11)	0.012	-9.52 (-18.17 to -0.87)	0.041

3.4. The impact of subgroup variables on the relationship between average GCL thickness and WMH severity

Stratified analysis was conducted to assess the impact of age, gender, BMI, hypertension, and diabetes on the relationship between GCL thickness and WMH severity. The results revealed a significant interaction effect for age ($P < 0.05$), indicating that the reducing effect of moderate-to-severe WMH on average GCL thickness varied across different age groups. In the subgroup of patients with type 2 diabetes, the correlation between moderate-to-severe WMH and reduced average GCL thickness was significantly enhanced ($\beta = -39.00$, 95% CI: -44.54 to -33.46, $P < 0.05$). No statistically significant interactions were observed in the subgroups stratified by gender, BMI, and hypertension ($P > 0.05$) (**Figure 2**).



Variables	n (%)	Mild WMH	Moderate severe WMH	β (95%CI)	P	P for interaction
		Mean (SE)				
All patients	31 (100.00)	85.33 ± 6.21	74.20 ± 16.12	-9.16 (-17.69 ~ -0.63)	0.046	
Gender						0.980
Male	17 (54.84)	86.50 ± 6.63	78.00 ± 6.78	-6.14 (-15.56 ~ 3.29)	0.228	
Female	14 (45.16)	83.78 ± 5.59	70.40 ± 22.41	1.63 (-17.37 ~ 20.64)	0.870	
Age						0.020
<60	13 (41.94)	87.80 ± 4.85	63.67 ± 26.63	-17.40 (-34.10 ~ -0.71)	0.080	
≥ 60	18 (58.06)	83.09 ± 6.66	78.71 ± 8.60	-3.75 (-13.20 ~ 5.70)	0.452	
BMI(kg/m2)						0.186
<24	15 (48.39)	84.09 ± 5.47	79.00 ± 6.38	-3.37 (-10.54 ~ 3.79)	0.380	
≥ 24	16 (51.61)	86.70 ± 6.96	71.00 ± 20.31	-14.16 (-28.19 ~ -0.12)	0.076	
HBP						0.850
No	16 (51.61)	86.40 ± 6.90	72.17 ± 20.47	-5.53 (-20.98 ~ 9.93)	0.499	
Yes	15 (48.39)	84.36 ± 5.66	77.25 ± 7.76	-1.76 (-14.07 ~ 10.55)	0.786	
T2DM						0.165
No	24 (77.42)	85.67 ± 6.65	80.50 ± 8.34	-4.93 (-11.78 ~ 1.91)	0.175	
Yes	7 (22.58)	83.33 ± 1.53	64.75 ± 21.56	-39.00 (-44.54 ~ -33.46)	0.046	

Figure 2. The impact of subgroup variables on the relationship between average GCL thickness and WMH severity

3.5. Predictive value of average GCL thickness for moderate-to-severe WMH

ROC curve analysis demonstrated that the area under the curve (AUC) for predicting moderate-to-severe WMH using average GCL thickness alone was 0.80 (95% CI: 0.62–0.99). After adjusting for age and gender, the AUC was 0.80 (95% CI: 0.63–0.98). Further adjustment for hypertension and diabetes increased the AUC to 0.83 (95% CI: 0.67–0.99), suggesting that average GCL thickness has good predictive value for moderate-to-severe WMH, and combining it with clinical factors can enhance predictive ability (**Figure 3**).

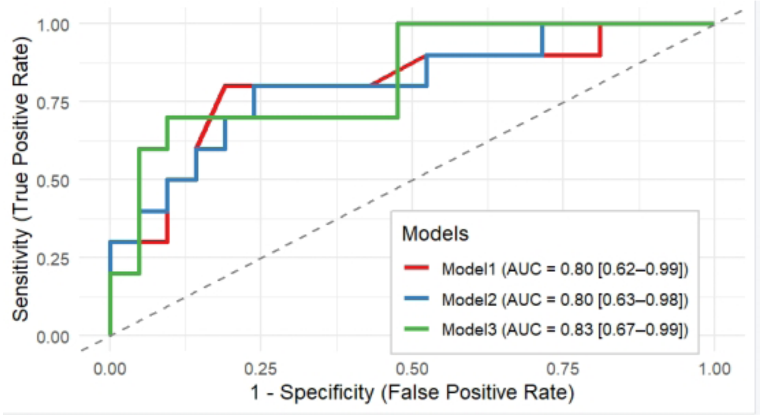


Figure 3. ROC curve for predicting moderate-to-severe WMH based on average GCL thickness

4. Discussion

Cerebral small vessel disease (CSVD) is a series of pathological, clinical, and imaging syndromes caused by multiple etiologies, affecting small cerebral vessels and brain parenchyma. CSVD often has an insidious onset with subtle clinical manifestations, frequently going unnoticed. Moreover, common clinical assessment and examination methods struggle to reflect the pathological state of intracranial vessels [7]. Therefore, this study employed OCT to analyze the correlation between GCL thickness and WMH severity in CSVD patients. The results revealed a significant negative correlation between WMH severity and average GCL thickness in CSVD patients. As the Fazekas score increased, indicating worsening WMH, GCL thickness progressively thinned. Furthermore, the average GCL thickness demonstrated good predictive value for moderate-to-severe WMH, consistent with the findings of Song et al. [8]. The underlying reason is that the retina and cerebral vessels share a common embryological origin from the mesoderm, and both microvascular systems lack collateral circulation from choroidal vessels, making them highly sensitive to ischemic and hypoxic injuries [9]. Cerebral microcirculation hypoperfusion, a key pathological mechanism of CSVD, leads to ischemic injury of the cerebral white matter, manifesting as the onset and progression of WMH. Simultaneously, systemic microcirculation pathological changes concurrently affect the retina, resulting in insufficient retinal microvascular perfusion, triggering apoptosis and degeneration of retinal ganglion cells, and ultimately leading to a reduction in GCL thickness [10].

In this study, the association between GCL thickness and WMH varied across different regions. Significant intergroup differences were observed in the average thickness and the thickness in the inferior nasal, inferior, and inferior temporal regions, while the difference in the superior temporal region did not reach statistical significance. This may be related to variations in blood supply distribution and sensitivity to ischemia across different retinal regions [11–12]. Additionally, subgroup analysis revealed that type 2 diabetes significantly enhanced the negative correlation between moderate-to-severe WMH and GCL thickness. Diabetic patients exhibit microcirculation disorders, leading to thickening of the microvascular basement membrane, narrowing of the lumen, and decreased blood flow perfusion. This not only exacerbates ischemic injury to the cerebral white matter, worsening WMH severity, but also further intensifies ischemic apoptosis of retinal ganglion cells, further reducing GCL thickness. Huang et al. demonstrated that CSVD patients with diabetes had more pronounced WMH, particularly deep WMH, and more significant reductions in retinal vessel density, corroborating the findings of this study [13]. Multivariate linear regression analysis showed a negative correlation between WMH severity and average GCL thickness. ROC curve analysis indicated that the corrected model had an AUC of 0.83 for predicting moderate-to-severe WMH, suggesting that average GCL thickness can serve as an effective predictor of moderate-to-severe WMH. As a non-invasive, convenient, and quantifiable detection technique, OCT offers advantages over expensive imaging examinations like cranial MRI, including ease of operation, low cost, absence of radiation, and the ability for repeated testing [14–15]. Clinically, OCT can be used to detect the average GCL thickness, indirectly assessing WMH severity in CSVD patients, stratifying patients based on imaging burden, reducing unnecessary cranial MRI examinations, and lowering medical costs.

5. Conclusion

In summary, GCL thickness in CSVD patients is negatively correlated with WMH severity, and average GCL thickness has good predictive value for moderate-to-severe WMH. Meanwhile, OCT, as a non-invasive retinal imaging technique, provides a new means for early identification of CSVD and assessment of cerebral white matter lesions. However, this study has certain limitations: (1) It is a single-center study with a relatively small sample size, which may affect the stability of the results; (2) The study population consisted of middle-aged and elderly individuals, and some subjects were excluded from analysis due to poor OCTA image quality caused by cataracts or other ocular diseases, potentially influencing the study results. Future research will involve multi-center, large-sample, prospective follow-up studies to further validate the correlation between GCL thickness and WMH progression in CSVD patients and clarify its value as a disease assessment biomarker.

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Disclosure statement

The authors declare no conflict of interest.

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