DEVELOPMENTAL MEDICO-LIFE-SCIENCES

ISSN (P): 3007-2786, (E): 3007-2794 DOI: https://doi.org/10.69750/dmls.02.05.0124

ORIGINAL RESEARCH ARTICLE Open Access

Correlation Between Retinal Nerve Fiber Layer Thickness and Cognitive Decline in Elderly Patients Using Optical Coherence Tomography (OCT)

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ABSTRACT

Background: Dementia and mild cognitive impairment are rising concerns in Pakistan's aging population, yet access to conventional neuroimaging and cerebrospinal fluid biomarkers is limited. Retinal imaging via optical coherence tomography (OCT) offers a non-invasive window into central nervous system health, with thinning of the retinal nerve fiber layer (RNFL) proposed as an early indicator of neurodegeneration.

Objective: To assess the relationship between peripapillary RNFL thickness as well as related retinal and systemic biomarkers and global cognitive function in elderly Pakistani patients.

Methods: In this cross-sectional study, 120 participants aged 65 years or older were recruited from Syed Eye Care (Bahawalpur) and Allied Hospital II (Faisalabad) and stratified by Mini-Mental State Examination score into cognitively normal (n=40), mild cognitive impairment (n=40), and dementia (n=40) groups. Spectral-domain OCT measured average and quadrant-specific RNFL thickness, ganglion cell–inner plexiform layer thickness, and central macular thickness. Blood samples were analyzed for Alzheimer's biomarkers ($A\beta_{42}$, total tau, phospho-tau), inflammatory marker (C-reactive protein), and vascular risk factors (homocysteine, cholesterol). Group comparisons utilized one-way ANOVA, and associations with cognitive scores were evaluated using Pearson correlation.

Results: Average RNFL thickness decreased progressively from 89.1 ± 4.7 µm in controls to 81.7 ± 5.2 µm in mild cognitive impairment and 72.4 ± 4.5 µm in dementia ($p < 0.001$). Similar graded reductions were observed in ganglion cell–inner plexiform layer and central macular thickness (all $p < 0.001$). Blood $A\beta_{42}$ declined and tau species, C-reactive protein, homocysteine, and cholesterol increased significantly across cognitive groups ($p < 0.01$). Temporal RNFL thickness demonstrated the strongest correlation with cognitive performance ($r = 0.66$, $p < 0.001$).

Conclusion: OCT-derived retinal measures, particularly temporal RNFL thickness, correlate strongly with cognitive impairment and systemic Alzheimer's and vascular biomarkers in Pakistani elders. OCT screening may serve as a practical, non-invasive adjunct for early detection of neurodegenerative change in resource-limited settings.

Keywords: optical coherence tomography; retinal nerve fiber layer; cognitive decline; Alzheimer's biomarkers; elderly; Pakistan.

Received: 17/06/2025
Revised: 10/07/2025
Accepted: 11/07/2025
Published: 12/07/2025

INTRODUCTION

Cognitive impairment and dementia are increasingly recognized as critical health issues in Pakistan, where the proportion of older adults is climbing rapidly. Over the past two decades, the share of Pakistan's population aged 60 and above has risen from just under 6 percent to nearly 9 percent, and current projections indicate it may approach 15 percent by 2050 [1]. This demographic shift brings into sharp focus the need for scalable strategies to identify and manage neurodegenerative conditions at their earliest stages. At present, an estimated 1.2 million Pakistanis live with some form of cognitive decline, yet formal diagnoses often occur late, when functional deficits have already eroded quality of life and independence [2].

The economic and social burdens of dementia in Pakistan are borne almost entirely by families. In the absence of widespread long-term care facilities, informal caregiving by spouses, children, or extended relatives consumes both time and financial resources [3]. Healthcare expenditure for geriatric services remains under 5 percent of the national health budget, and direct out-of-pocket payments account for over 70 percent of medical costs. As a result, many families are compelled to forgo early diagnostic workups such as neuroimaging or specialist consultations until symptoms become severe and unavoidable [4].

Advanced diagnostic modalities like magnetic resonance imaging and positron emission tomography are available only in a handful of urban tertiary centers, and each scan can cost upwards of PKR 50,000. Cerebrospinal fluid analysis for Alzheimer's biomarkers requires specialized laboratories found in fewer than ten institutions nationwide [5]. These barriers make routine screening and early detection of mild cognitive impairment impractical for the vast majority of older Pakistanis, particularly those living outside major metropolitan areas [6].

In contrast, optical coherence tomography (OCT) has become increasingly accessible in ophthalmology clinics across Pakistan. Over the last five years, more than 30 public and private hospitals have installed spectral-domain OCT devices, performing upwards of 100,000 retinal scans annually. With a per-scan cost of approximately PKR 5,000 and an acquisition time of under ten minutes, OCT presents a feasible option for integration into routine health checks for older adults, even in resource-constrained settings [7].

The retinal nerve fiber layer (RNFL) composed of axons from retinal ganglion cells shares embryological origins with the brain and undergoes thinning in parallel with neurodegenerative processes. Measuring RNFL thickness via OCT offers a non-invasive, quantitative glimpse into central nervous system health. In ophthalmology, RNFL assessment is already standard practice for glaucoma monitoring, demonstrating the technique's precision, reproducibility, and clinical utility [8].

Preliminary regional studies have revealed that up to one-third of Pakistani seniors with mild cognitive complaints exhibit RNFL thinning beyond age-matched norms, particularly in the temporal quadrant. Those with established dementia may show reductions of 15–18 percent in average RNFL thickness, while individuals with mild cognitive impairment often display losses of 8–10 percent. Nevertheless, these investigations have been limited by small sample sizes, heterogeneous cognitive classification criteria, and variable imaging protocols [9].

To bridge these gaps, there is an urgent need for a larger, standardized study that stratifies participants into cognitively normal, mild cognitive impairment, and dementia groups within the same cohort. By applying a

uniform spectral-domain OCT protocol and validated neuropsychological assessments, researchers can more accurately delineate the graded relationship between RNFL metrics and global cognitive function. This approach will also enable determination of optimal RNFL thresholds to distinguish early impairment from normal aging [10].

In the present study, current study aim to assess the correlation between peripapillary RNFL thickness and cognitive performance in a well-characterized cohort of Pakistani elders. Current study objectives are to compare average and quadrant-specific RNFL measurements across cognitive categories, quantify their association with standardized cognitive scores, and evaluate the diagnostic accuracy of OCT-derived biomarkers for early neurodegenerative change. Demonstrating the feasibility and utility of OCT screening in this context could transform current paradigms of cognitive health in Pakistan, enabling timely intervention, reducing caregiver burden, and improving long-term outcomes for our aging population [11].

MATERIALS AND METHODS

This cross-sectional observational study was carried out between June 2024 and May 2025 at two tertiary ophthalmic centres in Punjab, Pakistan: Syed Eye Care, Syed Medical Centre, Bahawalpur, and the Department of Ophthalmology at Allied Hospital II, Faisalabad. Ethical clearance was obtained from the institutional review boards of both institutions, and written informed consent was secured from each participant prior to enrolment.

Consecutive patients aged 65 years or older presenting to the outpatient clinics were evaluated for eligibility. Inclusion criteria comprised age 65 years or above, the ability to complete cognitive testing, and clear ocular media permitting high-quality imaging. Exclusion criteria were a history of glaucoma or optic neuropathy, retinal vascular disease (including diabetic or hypertensive retinopathy), prior intraocular surgery within the preceding six months (except for uncomplicated cataract extraction more than six months earlier), high refractive error (spherical equivalent beyond ±5.0 diopters), and any neurological or ophthalmic comorbidity likely to influence retinal nerve fiber layer (RNFL) measurements. Demographic details, systemic medical history, current medications, and best-corrected visual acuity were recorded for all participants.

Global cognitive function was assessed at each site by a neurologist fluent in Urdu, using the Mini-Mental State Examination (MMSE) adapted to local norms. Participants were stratified into three groups based on MMSE score: cognitively normal (MMSE $\geq$ 27), mild cognitive impairment (MMSE 21–26), and dementia (MMSE $\leq$ 20). Testing was conducted in a quiet room, and any participant exhibiting acute delirium or sensory impairment precluding valid administration was excluded.

Peripapillary RNFL thickness was measured using a spectral-domain OCT device (Cirrus HD-OCT, Carl Zeiss Meditec) at both sites to ensure uniformity. Certified ophthalmic technicians performed imaging under standardized ambient illumination. A 3.4 mm diameter circular scan centred on the optic nerve head was acquired for each eye. Only scans with signal strength of seven or greater, free of motion artefacts and segmentation errors, were included. Quadrant-specific RNFL thickness values (superior, inferior, nasal, and temporal) and the overall average RNFL thickness were recorded. For each participant, measurements from the right and left eyes were averaged to yield a single value per quadrant and a composite mean RNFL thickness.

All data were entered into a secure database and analysed using SPSS version 25.0. Continuous variables are expressed as mean ± standard deviation, and categorical data as frequencies with percentages. One-way analysis of variance (ANOVA) with Tukey's post-hoc test was applied to compare RNFL thickness across the three cognitive groups. Pearson's correlation coefficient was used to explore the relationship between MMSE scores and RNFL measurements. Statistical significance was defined as a two-tailed p-value < 0.05.

RESULTS

Participant Demographics:

A total of 120 participants were enrolled, evenly distributed across the three cognitive groups. The mean age was similar between groups ($p = 0.45$), and gender balance was maintained ($p = 0.95$). Educational attainment declined markedly with worsening cognition, and vascular risk factors including hypertension, diabetes, and hyperlipidemia increased stepwise from controls to MCI to dementia (all $p < 0.05$), whereas body mass index and smoking history did not differ significantly ($p = 0.12$ and $p = 0.30$, respectively) as shown in table 1.

Table 1: Extended Participant Demographics

Variable	Cognitively Normal (n = 40)	MCI (n = 40)	Dementia (n = 40)	p-value
Age, years	70.8 ± 4.1	71.6 ± 4.5	71.8 ± 4.4	0.45
Gender (M/F)	21/19	20/20	21/19	0.95
Education, years	12.2 ± 3.1	8.5 ± 2.8	5.7 ± 3.3	< 0.001
Body Mass Index (kg/m²)	24.5 ± 2.8	25.1 ± 3.2	25.7 ± 3.5	0.12
Hypertension, n (%)	14 (35%)	18 (45%)	24 (60%)	0.03
Diabetes Mellitus, n (%)	12 (30%)	16 (40%)	22 (55%)	0.04
Hyperlipidemia, n (%)	6 (15%)	9 (22.5%)	14 (35%)	0.02
Smoking History, n (%)	8 (20%)	10 (25%)	12 (30%)	0.30

OCT-Derived Retinal and Macular Biomarkers:

Spectral-domain OCT revealed progressive thinning of the RNFL, ganglion cell–inner plexiform layer (GCIPL), and central macula with worsening cognitive status (all $p < 0.001$). Average RNFL thickness fell by 8 µm in MCI and an additional 9 µm in dementia compared to controls. GCIPL thickness exhibited a similar trajectory, while central macular thickness decreased by approximately 15 µm across the cognitive spectrum as shown in table 2.

Table 2: OCT-Derived Retinal Biomarkers

Parameter	Cognitively Normal Mean ± SD (µm)	MCI Mean ± SD (µm)	Dementia Mean ± SD (µm)	p-value
Average RNFL	89.1 ± 4.7	81.7 ± 5.2	72.4 ± 4.5	< 0.001
Ganglion Cell–Inner Plexiform Layer	81.3 ± 5.7	73.5 ± 6.2	65.4 ± 5.9	< 0.001
Central Macular Thickness	275.6 ± 12.3	268.9 ± 13.5	260.2 ± 14.1	< 0.001

Systemic Blood Biomarkers:

Blood assays demonstrated classical Alzheimer's and vascular risk profiles that paralleled retinal changes. Amyloid-β_{42} declined by over 30 percent from controls to dementia, while total tau and phospho-tau more than doubled. Inflammatory and vascular markers CRP, homocysteine, and cholesterol also increased significantly with cognitive impairment as shown in table 3.

Table 3. Systemic Blood Biomarkers

Biomarker	Cognitively Normal Mean ± SD	MCI Mean ± SD	Dementia Mean ± SD	p-value
$A\beta_{42}$ (pg/mL)	45.6 ± 7.8	38.2 ± 6.9	31.5 ± 7.2	< 0.001
Total Tau (pg/mL)	230.5 ± 40.2	302.6 ± 55.3	384.7 ± 60.1	< 0.001
Phospho-Tau (pg/mL)	23.4 ± 5.1	31.7 ± 6.4	42.9 ± 7.5	< 0.001
C-Reactive Protein (mg/L)	2.1 ± 0.9	3.4 ± 1.2	5.6 ± 2.3	< 0.001
Homocysteine (µmol/L)	12.3 ± 3.4	14.8 ± 4.1	18.2 ± 5.0	< 0.001
Total Cholesterol (mg/dL)	180.2 ± 25.3	192.5 ± 28.4	205.7 ± 30.6	0.005

Correlation Between Retinal Measures and Cognitive Function:

Pearson correlation analysis confirmed that thinner RNFL was strongly associated with lower MMSE scores. Temporal quadrant thickness showed the highest correlation, suggesting its particular vulnerability in neurodegeneration as shown in table 4.

Table 4. Correlation Between RNFL Thickness and MMSE Score

RNFL Parameter	Pearson r	p-value
Average	0.61	< 0.001
Superior	0.54	< 0.001
Inferior	0.49	< 0.001
Nasal	0.32	0.04
Temporal	0.66	< 0.001

These results demonstrate that retinal thinning and macular degeneration, as quantified by OCT, correspond closely with cognitive impairment and systemic Alzheimer's and vascular biomarkers. The graded decline in ocular measures across cognitive stages, coupled with their strong correlation to MMSE scores, underscores the potential of OCT as a non-invasive, accessible screening tool for early neurodegenerative change in Pakistan's elderly population.

DISCUSSION

In this study of 120 elderly Pakistani patients, we observed a clear, graded relationship between retinal structural integrity as measured by OCT and cognitive status. Average RNFL thickness declined by nearly 20 μm from cognitively normal controls to patients with dementia, with intermediate values in those with mild cognitive impairment [12]. Parallel reductions in GCIPL and central macular thickness further indicate that neuronal loss extends beyond the peripapillary region into the macula. These ocular findings align closely with systemic biomarker changes: progressive lowering of $A\beta_{42}$, elevations in total and phospho-tau, and increases in C-reactive protein, homocysteine, and cholesterol, all of which have been implicated in Alzheimer's pathology and cerebrovascular dysfunction. The convergence of retinal and blood-based markers strengthens the hypothesis that retinal neurodegeneration mirrors cerebral amyloid-tau accumulation as well as vascular and inflammatory contributions to cognitive decline [13].

Quadrant analysis revealed the temporal RNFL to be particularly sensitive to cognitive impairment, exhibiting the strongest correlation with MMSE scores. This may reflect selective vulnerability of the maculopapillary fiber bundle, which subserves central vision and contains a high density of small-caliber axons prone to early degeneration. The superior and inferior quadrants also demonstrated significant thinning, whereas nasal thinning was less pronounced. These spatial patterns may offer insight into disease staging and suggest that temporal measurements could serve as the most discriminating OCT parameter for early screening [14, 15].

Our demographic data highlight important co-factors in this population. Patients with lower educational attainment and higher prevalence of hypertension, diabetes, and hyperlipidemia were more likely to exhibit cognitive impairment and retinal thinning. This underscores the multifactorial nature of neurodegeneration in real-world settings, where vascular risk factors and cognitive reserve both modulate disease expression. Integrating vascular risk assessment and cognitive testing with retinal imaging could therefore enhance predictive models and inform individualized preventive strategies [16].

Several limitations warrant consideration. The cross-sectional design precludes causal inference and limits assessment of longitudinal change. Although MMSE is a well-validated tool for global cognition, it lacks sensitivity for certain domains and may be influenced by education level; future studies should incorporate comprehensive neuropsychological batteries. Our cohort, drawn from two tertiary eye-care centres, may not fully represent rural or lower-socioeconomic populations. Moreover, while OCT measurements were standardized across sites, inter-device calibration and variability in scan quality remain potential sources of measurement error [17, 18].

Despite these limitations, our findings have important clinical implications. OCT is widely available, non-invasive, and relatively low-cost compared with MRI, PET, or CSF assays, making it well-suited for screening older adults in both urban and resource-limited settings. Temporal RNFL thickness, in

particular, may serve as a practical biomarker to flag individuals who would benefit from further cognitive evaluation or early intervention. Longitudinal studies are now needed to determine whether baseline retinal changes predict subsequent cognitive decline and conversion to Alzheimer's disease [19, 20].

CONCLUSION

This study demonstrates that retinal nerve fiber layer thinning, along with reductions in GCIPL and macular thickness, correlates strongly with cognitive impairment and systemic Alzheimer's-related and vascular biomarkers in an elderly Pakistani cohort. Temporal RNFL measurements showed the highest association with MMSE scores, suggesting their utility as an early, non-invasive screening marker. Given its accessibility and efficiency, OCT has the potential to augment current cognitive screening paradigms, particularly in settings where advanced neuroimaging and biomarker assays are impractical. Future longitudinal and multicentre research should further validate OCT-derived retinal metrics as predictors of cognitive decline and integrate them into comprehensive risk-stratification frameworks for neurodegenerative disease.

Conflict of Interest:

HSUAR, SA, IM, and SAHW declare that they have no conflicts of interest related to this study. No financial, personal, or professional affiliations influenced the conduct or reporting of this research.

Funding:

No external funding was received for this study. All research-related expenses were borne by the authors and their affiliated institutions.

Acknowledgements:

The authors express their sincere appreciation to the ophthalmic technicians and neurology departments at Syed Eye Care, Bahawalpur, and Allied Hospital II, Faisalabad, for their invaluable technical support. Special thanks to all elderly participants and their families for their cooperation and trust.

Authors' Contributions:

HSUAR: Study design, patient enrolment, clinical assessment, and manuscript drafting.

SA: Data collection, OCT imaging supervision, and preliminary analysis.

IM: Oversight of OCT protocol standardization, clinical interpretation, and manuscript review.

SAHW: Data analysis, statistical evaluation, results interpretation, and final manuscript editing.

All authors read and approved the final version of the manuscript.

Availability of Data and Materials:

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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This Article May be cited As: *Rehman HSUA, Ahmad S, Manzoor I, Subzwari SAHW. Correlation Between Retinal Nerve Fiber Layer Thickness and Cognitive Decline in Elderly Patients Using Optical Coherence Tomography (OCT): OCT-Based Retinal Markers for Cognitive Decline. DEVELOPMENTAL MEDICO-LIFE-SCIENCES. 2025;2(5):4-12.doi: 10.69750/dmls.02.05.0124.*