Original Article

Peripapillary Retinal Nerve Fiber Layer Thickness and its Ocular and Systemic Determinants in an Elderly Population: A Population-Based Study

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Abstract

Purpose: To determine the distribution, ocular, and systemic determinants of peripapillary retinal nerve fiber layer thickness (pRNFLT) using spectral-domain optical coherence tomography (SD-OCT) in an elderly population.

Methods: This report is a part of the Tehran Geriatric Eye Study, a population-based cross-sectional study conducted in Tehran, the capital of Iran. The study population was all residents aged 60 years and above in Tehran. The sampling was performed using a multi-stage stratified random cluster sampling method. All study participants underwent ocular examination (including measurement of visual acuity, objective and subjective refraction, and slit-lamp biomicroscopy), anterior segment imaging using Pentacam HR, and ocular biometry using IOLMaster 500. The OCT imaging was performed for a random subsample (1307 individuals) using Spectralis SD-OCT.

Results: Two thousand two hundred and forty-six eyes of 1189 individuals were analyzed for this report. Of these, 691 (58.1%) were female, and the mean age of the participants was 67.3 ± 5.9 years (60–94 years). The mean overall pRNFLT was 98.6 μ (95% confidence interval [CI]: 98.0–99.3). There was a statistically significant difference in pRNFLT between different quadrants; the highest and lowest mean pRNFLT was related to inferior and temporal quadrants, respectively ($P < 0.001$). The multiple generalized estimating equation model showed that older age (coefficient: −0.15 [95% CI: −0.24 to −0.06], $P = 0.001$), diabetes (coefficient: −1.69 [95% CI: −2.82 to −0.55], $P = 0.004$), and longer axial length (coefficient: −0.52 [95% CI: −0.83 to −0.22], $P < 0.001$) were significantly associated with a decreased overall pRNFLT. Higher body mass index was significantly related to an increased overall pRNFLT (coefficient: 0.19 [95% CI: 0.07 to 0.30], $P = 0.002$).

Conclusions: The results of the present study can be used as a reference database for pRNFLT in the elderly population. Considering ocular and systemic determinants of pRNFLT is necessary for correct clinical interpretation of this parameter.

Keywords: Elderly population, Ocular determinants, Peripapillary retinal nerve fiber layer thickness, Population-based study, Systemic determinants

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Introduction

Evaluation of peripapillary retinal nerve fiber layer thickness (pRNFLT) is an important part of diagnosing, monitoring the progression, and management of patients with glaucoma and other optic neuropathies since RNFL damage often precedes obvious morphologic optic disc change and visual field loss.[1] Today, clinical applications of pRNFLT have extended so that it is also used as a biomarker to identify neurodegenerative diseases such as cognitive impairment,

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Alzheimer's disease, and multiple sclerosis.[2,3] The introduction of optical coherence tomography (OCT) has enabled *in vivo* cross-sectional imaging of the retina and the optic nerve as well as quantitative assessment of pRNFLT with high accuracy and reproducibility.[4] Recently, OCT technology has been evolved through spectral-domain OCT (SD-OCT) which improves depth resolution by a factor of 2 and shortens the acquisition time, creating a substantial improvement in image quality.[5]

Normal pRNFLT data are important for correctly interpreting pRNFLT measurements and knowing what changes are within the physiological range for an individual.[6] Therefore, various population-based studies have examined the distribution of pRNFLT in different populations.[7] Accordingly, most OCT instruments are equipped with normative reference databases to facilitate clinical pRNFLT interpretation. However, most previous studies on pRNFLT distribution had a wide age range and were mostly related to Western or East Asian populations.[8,9] There are limited pRNFLT data in the Middle East countries including Iran; this is while previous studies have pointed to racial differences in pRNFLT.[10,11] The pRNFLT decreases by an average of 0.18% per year of advancing age, which corresponds to an average thinning of 2 μ per decade.[12] Despite age-related changes in RNFL thickness, little is known about pRNFLT in the general elderly population.[13] Most previous studies included a small proportion of elderly subjects.[11,14-19] Limited studies have examined the distribution of pRNFLT specifically in the elderly,[13,20,21] which also had a small sample size. Due to the increased prevalence of glaucoma and other optic neuropathies with advancing age,[22] older adults (≥60 years) constitute a significant percentage of patients, in whom pRNFLT evaluations are indicated.

In addition to age, different ocular and systemic factors have been introduced as determinants of pRNFLT in the literature.[8,9,11,23-25] However, previous studies have reported conflicting results for many ocular and systemic factors.[8] A possible reason for these discrepancies is that most previous studies examined limited factors and the confounding effects of different indicators were not efficiently controlled by a comprehensive multivariable analysis. Moreover, the majority of large-scale studies assessing these associations were performed in young populations. According to the above, the present population-based study aimed to investigate the distribution of pRNFLT and its associated ocular and systemic factors using SD-OCT in an Iranian elderly population.

Methods

This report is a part of the Tehran Geriatric Eye Study (TGES), a population-based cross-sectional study conducted in 2019 in Tehran city, the capital of Iran. The target population was all residents aged 60 years and above in Tehran. Informed consent was obtained from all participants. The principles of the Declaration of Helsinki were followed in all stages of this study. The protocol of the study was approved by the Ethics Committee of the Iran University of Medical Sciences under the auspices of the Iranian Ministry of Health (ethics code: IR.IUMS.REC.1400.1199).

The sampling was performed using a multi-stage stratified random cluster sampling method. First, each of the 22 municipality districts of Tehran was considered strata and the population ≥60 years in each district was obtained from the National Statistics Center. Then, a block map of each district was prepared and each block was considered a cluster. A total of 160 clusters with a size of 20 individuals were randomly selected from all 22 districts of Tehran; the number of clusters in each district was proportional to the population of that district (proportion to size). After identifying the clusters, a sampling team was sent to the address of each cluster and located on the southwest side of the selected block, and the first house was selected as the head of the cluster. Then, by moving counterclockwise while selecting the next households, all individuals 60 years of age and above were invited to participate in the study after explaining the objectives of the study and ensuring the confidentiality of the information. This process continued until the sample size in each cluster was completed. The study participants were transferred to the examination site (Noor Eye Hospital) free of charge on a prescheduled day. Once the study participants presented to the study site, a preliminary interview was performed to collect information on the history of ocular and systemic diseases, history of previous ocular surgery, history of stroke (cerebral infarction), use of ocular and systemic medications, and smoking. In the next step, the body mass index (BMI) was calculated following height and weight measurements using the formula: Weight (kg)/height (m)^2. The blood pressure was measured twice at a 10-minute interval using sphygmomanometry (OMRON, HEM-2228-E, Kyoto, Japan) in a sitting position with the arm supported on a table at heart level, and the average values were recorded. A third measurement was performed if the two differed by ≥10 mmHg in systolic blood pressure or ≥5 mmHg in diastolic blood pressure. In this case, the average of two closer values was considered. Then, blood samples were taken for laboratory tests to measure glycosylated hemoglobin (HbA1c), blood hemoglobin, and cholesterol levels.

The uncorrected distance visual acuity was measured using a LED visual acuity chart (Smart LC 13, Medizs Inc., Korea) at 6 m. The objective refraction was performed using an auto-refractometer (ARK-510A, Nidek Co. 42 Ltd., Aichi, Japan). The subjective refraction was performed to determine the optimal distance optical correction, and the best-corrected distance visual acuity (BCVA) was recorded.

In the next step, all study participants underwent anterior segment imaging using the Pentacam HR (Oculus, Wetzlar, Germany). Images were obtained using automatic 50-image scan mode, and only measurements were considered valid that displayed "OK" in the scan quality specification box. Information on mean keratometry (mean K) at the central 4 mm zone and central corneal thickness (CCT) at the pupil

center were extracted and recorded. Three high-quality axial length (AL) measurements with a signal-to-noise ratio above 2.0 were performed using IOLMaster 500 (Carl Zeiss Meditec AG, Jena, Germany) before cycloplegia, and the average of three measurements was considered the final AL.

Due to cost and time considerations, OCT imaging was performed for a random subsample (about 40% of the whole sample: 1307 individuals) with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) following cycloplegia with two drops of tropicamide 1%. This instrument is a combination of conventional OCT technology and confocal scanning laser ophthalmoscopy and uses a superluminescence diode to emit a laser scan beam of 870 nm. The RNFL optic disc protocol was used to measure the pRNFLT consisting of a circle scan centered on the optic disc. The fovea-to-disc alignment technology was also applied to help overcome measurement errors resulting from changing head/eye position during scanning. The circle scan contains 1536 A-scan points from a 12-degree circle, which corresponds to a retinal diameter of 3.5–3.6 mm in eyes with standard corneal curvature. The acquisition rate is 40000 A-scans per second at an axial resolution of approximately 3.9 mm and a lateral resolution of 6 mm. The device uses a real-time eye-tracking system to compensate for the involuntary eye movements that may occur during imaging. Automatic segmentation of the upper and lower RNFL borders is also provided to calculate the overall average pRNFLT. The pRNFLT values are also separately presented in four quadrants; superior, inferior, nasal, and temporal. The software also provides a quality score indicating signal strength and ranges from 0 dB (poor) to 40 dB (excellent).

Finally, all study participants underwent complete anterior and posterior segment ocular examination by a glaucoma specialist using slit-lamp biomicroscopy (Haag-Streit AG, Bern, Switzerland) and a +90 diopter (D) lens. The intraocular pressure (IOP) was measured using Goldmann applanation tonometry.

Refractive errors were defined based on the spherical equivalent (SE) of objective refraction. The SE worse than −0.50 D and +0.50 D was defined as myopia and hyperopia, respectively. Diabetes mellitus (DM) was diagnosed based on the participant's self-report, antidiabetic treatment, or HbA1c level equal to or above 6.5%.[26] Systemic hypertension (HTN) was defined based on the participant's self-report, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or reported use of antihypertensive medication.[27] Hypercholesterolemia (HC) was defined based on the participant's self-report, a blood total cholesterol level of >200 mg/dL, or reported use of cholesterol-lowering medication.[28] Anemia was defined as blood hemoglobin concentration <12 g/dL in women and <13 g/dL in men.[29] Current smoking was defined as smoking at least one cigarette per day lasting for at least 6 months.

Exclusion criteria were BCVA worse than 20/40, history of ocular trauma, history of glaucoma, history of intraocular surgery other than uneventful cataract surgery, evidence of secondary causes of glaucoma (pseudoexfoliation, uveitis, and pigment dispersion syndrome), IOP >21 mmHg, history of retinal/optic nerve disease or ophthalmoscopic signs of retinal/optic nerve disease (including vertical cup/disc ratio >0.5 or asymmetric cup/disk ratio >0.2 and neuroretinal rim loss), and OCT quality score <15 dB.

Statistical analysis

The mean and 95% confidence interval (CI) of the overall pRNFLT and pRNFLT in superior, inferior, nasal, and temporal quadrants were reported. The effect of cluster sampling was considered in calculating the CIs. The pRNFLT of different quadrants was compared using repeated-measures analysis of variance (ANOVA). Independent-samples *t*-test was used for comparison of pRNFLT between sex groups. One-way ANOVA and Scheffe *post hoc* test were used for comparison of pRNFLT between age groups as well as refractive groups.

The simple and multiple generalized estimating equation (GEE) models were used to investigate the associations between pRNFLT and studied variables. The following demographic, ocular, and systemic factors were selected as the independent variables of the GEE models based on the literature review: age, sex, BMI, smoking status, DM, HTN, HC, anemia, history of stroke, history of cataract surgery, AL, CCT, mean K, and IOP. The multiple model was run using a backward-stepwise manner by entering all independent variables into the model and removing nonsignificant variables one by one in order of highest *P* values, with only statistically significant variables retained in the final model. $P < 0.05$ was considered statistically significant. Both eyes of each individual were included in the analysis.

Results

Three thousand three hundred ten of the 3791 invitees participated in the TGES (response rate, 87.3%). The OCT imaging was performed for 1307 participants. After applying the exclusion criteria, 2246 eyes of 1189 individuals were analyzed. Of these, 691 (58.1%) were female, and the mean age of the participants was 67.3 ± 5.9 years (60–94 years). Table 1 shows the distribution of the baseline ocular and systemic characteristics of the studied sample.

Table 2 presents the mean (95% CI) of the overall pRNFLT and the pRNFLT in different quadrants by age, sex, and refractive status. As shown in Table 2, females had statistically significantly thicker overall pRNFLT and sectoral pRNFLT in inferior and nasal quadrants compared to males. Moreover, the overall and sectoral pRNFLT (except for the temporal quadrant) decreased significantly with advancing age from the age group 60–64 years to the age group ≥80 years. A statistically significant difference was observed in the average and sectoral pRNFLT (except for the temporal quadrant) between refractive groups; myopes had the lowest thicknesses.

The 5th, 25th, 75th, and 95th percentiles of pRNFLT by age, sex, and refractive error are shown in Table 3. There was a statistically significant difference in pRNFLT between different quadrants; the highest and lowest mean pRNFLT was related to inferior and temporal quadrants, respectively ($P < 0.001$).

Table 1: Distribution of the baseline ocular and systemic characteristics of the sample

Parameter	Right eye	Left eye
	Mean±SD	Mean±SD
Continuous variables		
BMI (kg/m^2)	28.76±4.54	28.77±4.56
AL (mm)	23.19±0.96	23.2±1.28
CCT (μ)	527.45±31.24	525.4±30.75
Mean keratometry (D)	44.68±1.63	44.72±1.72
IOP (mmHg)	15±2.09	15.06±2.05
Categorical variables, *n* (%)		
DM	370 (31.1)	
HTN	973 (81.8)	
Anemia	19 (1.6)	
Current smoking	159 (13.4)	
History of stroke	176 (14.8)	
Cataract surgery	238 (20.0)	

SD: Standard deviation, BMI: Body mass index, AL: Axial length, CCT: Central corneal thickness, IOP: Intraocular pressure, DM: Diabetes mellitus, HTN: Systemic hypertension

Table 4 shows the results of simple GEE models for the associations of pRNFLTs with different study variables. The results of multiple GEE models are shown in Table 5. According to the multiple GEE model, older age was significantly associated with reduced overall pRNFLT and pRNFLT in superior and inferior quadrants. A statistically significant inverse relationship was found between DM with overall pRNFLT and pRNFLT in superior, inferior, and nasal quadrants. There was a statistically significant inverse relationship between AL with overall pRNFLT and pRNFLT in all quadrants except the temporal quadrant. The BMI had a statistically significant direct association with the overall pRNFLT and RNFLT in superior, inferior, and nasal quadrants. The mean K was significantly inversely associated with pRNFLT in the temporal quadrant. A statistically significant inverse association was found between temporal pRNFLT and a history of stroke. The history of cataract surgery was significantly associated with a thicker pRNFLT in the temporal quadrant. Other variables including sex, current smoking,

Table 2: The mean (95% confidence interval) of peripapillary retinal nerve fiber layer thickness (μ) by age, sex, and refractive status

	Overall pRNFLT	Superior pRNFLT	Inferior pRNFLT	Nasal pRNFLT	Temporal pRNFLT
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Total	98.6 (98.0–99.3)	122.1 (121.0–123.2)	127.1 (126.2–128.1)	75.2 (74.4–76.0)	70.2 (69.4–71.0)
Sex					
Male	97.9 (96.9–98.9)	121.7 (120.0–123.4)	125.7 (124.3–127.0)	74.5 (73.4–75.7)	69.9 (68.7–71.0)
Female	99.4 (98.6–100.2)	122.5 (121.1–123.8)	128.7 (127.5–129.9)	75.9 (74.9–76.9)	70.6 (69.6–71.5)
P	**<0.001**	0.055	**<0.001**	**0.023**	0.740
Age group (years)					
60–64	99.9 (99.0–100.8)	125.1 (123.4–126.7)	128.9 (127.6–130.2)	75.1 (73.8–76.3)	70.3 (69.3–71.4)
65–69	98.2 (97.2–99.2)	121.4 (119.7–123.2)	127.2 (125.8–128.7)	75.6 (74.3–76.9)	68.9 (67.8–70.0)
70–74	98.3 (97.0–99.5)	121.3 (119.2–123.3)	125.6 (123.7–127.5)	75.9 (74.1–77.7)	70.3 (68.8–71.8)
75–79	98.0 (95.6–100.3)	118.5 (114.3–122.7)	126.5 (123.3–129.6)	75.4 (73.0–77.7)	71.8 (68.8–74.7)
≥80	95.3 (91.4–99.2)	114.6 (109.5–119.7)	121.8 (115.5–128.0)	72.8 (69.3–76.3)	72.0 (67.3–76.7)
P	**<0.001**[a]	**<0.001**[b]	**<0.001**[c]	**0.046**[d]	0.085
Refractive status					
Emmetropia	98.9 (98.0–99.9)	122.5 (121.0–124.1)	127.0 (125.6–128.4)	75.5 (74.3–76.7)	70.5 (69.4–71.7)
Myopia	96.5 (95.0–98.0)	118.1 (115.6–120.6)	122.9 (120.9–125.0)	74.1 (72.4–75.8)	70.9 (69.0–72.7)
Hyperopia	99.5 (98.6–100.4)	123.8 (122.2–125.3)	129.5 (128.1–130.8)	75.5 (74.3–76.6)	69.6 (68.7–70.6)
P	**<0.001**[e]	**<0.001**[f]	**<0.001**[g]	**0.007**[h]	0.089

[a]Statistically significant differences were found when comparing 60–64 years with 65–69 years (P=0.024) and 60–64 years with ≥80 years (P<0.001); Scheffe *post hoc* test, [b]Statistically significant differences were found when comparing 60–64 years with 65–69 years (P=0.002), 60–64 years with 70–74 years (P=0.012), 60–64 years with 75–79 years (P<0.001), and 60–64 years with ≥80 years (P<0.001); Scheffe *post hoc* test, [c]Statistically significant differences were found when comparing 60–64 years with 70–74 years (P=0.005), 60–64 years with ≥80 years (P<0.001), and 65–69 years with ≥80 years P=0.006); Scheffe *post hoc* test, [d]Statistically significant differences were found when comparing 65–69 years with ≥80 years (P=0.044) and 70–74 years with ≥80 years (P=0.048); Scheffe *post hoc* test, [e]Statistically significant differences were found when comparing myopia with emmetropia (P=0.001) and myopia with hyperopia (P<0.001); Scheffe *post hoc* test, [f]Statistically significant differences were found when comparing myopia with emmetropia (P=0.002) and myopia with hyperopia (P<0.001); Scheffe *post hoc* test, [g]Statistically significant differences were found when comparing myopia with emmetropia (P=0.002), hyperopia with emmetropia (P=0.002), and hyperopia with myopia (<0.001); Scheffe *post hoc* test, [h]Statistically significant differences were found when comparing myopia with emmetropia (P=0.023) and myopia with hyperopia (P=0.011); Scheffe *post hoc* test. Bold values are statistically significant (P<0.05), Independent samples *t*-test was used for comparison of pRNFLT between sex groups, one-way analysis of variance was used for comparison of pRNFLT between age groups as well as refractive groups. pRNFLT: Peripapillary retinal nerve fiber layer thickness, CI: Confidence interval

Table 3: The 5th, 25th, 75th, and 95th percentiles of peripapillary retinal nerve fiber layer thickness (μ) by age, sex, and refractive status

	Overall pRNFLT	Superior pRNFLT	Inferior pRNFLT	Nasal pRNFLT	Temporal pRNFLT
	5th; 25th; 75th; 95th	5th; 25th; 75th; 95th	5th; 25th; 75th; 95th	5th; 25th; 75th; 95th	5th; 25th; 75th; 95th
Total	83.0; 92.0; 105.0; 115.0	95.4; 112.0; 133.0; 150.0	102.0; 118.0; 137.0; 154.0	55.0; 66.0; 84.0; 98.0	52.0; 62.0; 77.0; 90.0
Sex					
Male	81.0; 91.0; 104.5; 115.0	93.0; 110.0; 133.0; 150.0	101.0; 115.0; 135.0; 152.5	54.5; 65.0; 83.0; 98.0	51.0; 62.0; 77.0; 89.5
Female	84.0; 93.0; 106.0; 115.0	97.0; 113.0; 134.0; 150.0	104.0; 120.0; 138.0; 154.0	55.0; 66.0; 84.0; 99.0	53.0; 62.0; 77.0; 91.0
Age group (years)					
60–64	85.0; 94.0; 106.0; 116.0	99.0; 114.0; 136.0; 154.0	105.0; 120.0; 138.0; 154.0	53.6; 66.0;84.0; 98.0	53.0; 62.0; 76.0; 90.0
65–69	82.0; 92.0; 104.0; 114.0	94.2; 110.0; 132.0; 148.0	102.0; 118.0; 137.0; 153.0	57.0; 66.0; 84.0; 98.0	52.0; 61.0; 76.0; 90.0
70–74	81.8; 92.0; 105.0; 113.2	96.0; 112.0; 132.0; 147.0	99.8; 116.0; 136.0; 153.0	56.0; 67.0; 83.0; 101.2	52.0; 61.0; 78.0; 92.2
75–79	80.0; 90.0; 106.0; 117.0	84.3; 106.0; 132.2; 146.0	98.1; 114.0; 138.0; 157.8	55.0; 65.0; 84.2; 96.0	49.0; 62.0; 80.0; 97.7
≥80	77.0; 87.0; 103.0; 111.5	90.8; 108.0; 124.0; 146.2	91.8; 109.0; 133.0; 148.6	51.8; 61.0; 79.0; 96.4	50.0; 63.0; 82.0; 90.8
Refractive status					
Emmetropia	84.0; 93.0; 105.0; 114.0	97.0; 112.7; 134.0; 148.0	101.0; 118.0; 137.0; 152.6	55.0; 66.0; 84.0; 98.6	53,0; 62.0; 77.0; 90.0
Myopia	80.0; 89.0; 104.0; 114.2	91.8; 108.0; 130.0; 149.2	97.0; 114.0; 134.0; 149.0	54.0; 64.0; 82.0; 98.0	53,0; 62.0; 78.0; 93.2
Hyperopia	83.0; 93.0; 106.0; 116.0	98.0; 113.0; 134.0; 152.0	104.0; 120.0; 139.0; 157.0	55.3; 67.0; 84.0; 98.0	52.0; 61.0; 76.0; 89.0

pRNFLT: Peripapillary retinal nerve fiber layer thickness

Table 4: Association of peripapillary retinal nerve fiber layer thickness (μ) with study variables using simple generalized estimating equation models

Independent variable	Overall pRNFLT	Superior pRNFLT	Inferior pRNFLT	Nasal pRNFLT	Temporal pRNFLT
	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*
Age (year)	**−0.18 (−0.27– −0.1.0), <0.001**	**−0.39 (−0.54– −0.24), <0.001**	**−0.35 (−0.49– −0.21), <0.001**	−0.07 (−0.18–0.05), 0.262	0.08 (−0.02–0.18), 0.132
Sex (male/female)	**1.54 (0.47–2.62), 0.005**	1.49 (−0.30–3.28), 0.103	**3.14 (1.49–4.8), <0.001**	1.15 (−0.26–2.56), 0.109	0.23 (−1.02–1.49), 0.715
BMI (kg/m^2)	**0.22 (0.10–0.33), <0.001**	**0.28 (0.09–0.47), 0.004**	**0.35 (0.17–0.53), <0.001**	**0.21 (0.05–0.36), 0.008**	0.04 (−0.09–0.18), 0.551
Current smoking	−0.88 (−2.44–0.68), 0.271	−0.71 (−3.31–1.89), 0.593	−1.05 (−3.46–1.37), 0.395	−0.82 (−2.86–1.23), 0.435	−1.03 (−2.85–0.79), 0.266
DM	**−1.58 (−2.72– −0.43), 0.007**	**−3.01 (−4.91– −1.1), 0.002**	−1.73 (−3.51–0.04), 0.056	−1.30 (−2.81–0.2), 0.089	0.00 (−1.34–1.34), 0.998
HTN	0.08 (−1.3–1.46), 0.911	−0.36 (−2.65–1.94), 0.760	0.04 (−2.09–2.17), 0.972	0.81 (−1.00–2.61), 0.380	−0.12 (−1.73–1.49), 0.884
HC	2.38 (−1.55–6.31), 0.235	3.60 (−2.98–10.18), 0.283	3.00 (−3.28–9.28), 0.348	1.31 (−3.94–6.56), 0.625	1.32 (−3.41–6.06), 0.584
Anemia	−1.69 (−5.82–2.44), 0.422	0.53 (−6.44–7.5), 0.882	−2.41 (−8.92–4.11), 0.469	−4.12 (−9.78–1.54), 0.154	−0.76 (−5.77–4.26), 0.767
History of stroke	−0.90 (−2.39–0.6), 0.240	−0.56 (−3.05–1.93), 0.661	−1.32 (−3.64–0.99), 0.263	0.91 (−1.05–2.87), 0.362	**−2.55 (−4.29– −0.81), 0.004**
Cataract surgery	−0.30 (−1.31–0.71), 0.564	**−3.02 (−4.87– −1.18), 0.001**	**−2.12 (−3.88– −0.37), 0.018**	**−1.86 (−3.37– −0.36), 0.015**	**4.38 (3.08–5.68), <0.001**
AL (mm)	**−0.50 (−0.80– −0.20), 0.001**	**−1.37 (−1.95– −0.79), <0.001**	**−1.33 (−1.89– −0.76), <0.001**	**−0.71 (−1.2– −0.23), 0.004**	**0.55 (0.13–0.97), 0.010**
CCT (μ)	−0.01 (−0.03–0), 0.117	−0.02 (−0.05–0.01), 0.244	0.00 (−0.03–0.03), 0.979	−0.02 (−0.04–0.01), 0.128	−0.02 (−0.04–0), 0.106
Mean keratometry (diopter)	0.22 (−0.06–0.50), 0.122	**0.56 (0.07–1.05), 0.024**	**0.86 (0.4–1.31), <0.001**	0.38 (−0.01–0.77), 0.056	**−0.60 (−0.94– −0.25), 0.001**
IOP (mmHg)	0.10 (−0.14–0.33), 0.421	**0.46 (0.05–0.86), 0.026**	−0.06 (−0.44–0.32), 0.755	0.04 (−0.29–0.36), 0.821	−0.07 (−0.36–0.21), 0.614

Bold values are statistically significant ($P<0.05$). pRNFLT: Peripapillary retinal nerve fiber layer thickness, CI: Confidence interval, BMI: Body mass index, DM: Diabetes mellitus, HTN: Systemic hypertension, HC: Hypercholesterolemia, AL: Axial length, CCT: Central corneal thickness, IOP: Intraocular pressure

HTN, HC, anemia, CCT, and IOP did not show a statistically significant relationship with either of the pRNFLT values.

Discussion

The present population-based study investigated normal values of pRNFLT and its associated demographic, ocular, and systemic factors using Spectralis SD-OCT in a large sample of the Iranian elderly population. The mean overall pRNFLT was 98.6 μ in the present study. Table 6 shows a list of similar previous studies. Table 6 includes studies that either examined pRNFLT specifically in the elderly population[13,20,21] or had a wide age range but reported the mean overall pRNFLT separately in individuals above 60 years of age.[11,14-19]

Table 5: Association of peripapillary retinal nerve fiber layer thickness (μ) with study variables using backward-stepwise multiple generalized estimating equation models

Independent variable	Overall pRNFLT	Superior pRNFLT	Inferior pRNFLT	Nasal pRNFLT	Temporal pRNFLT
	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*	Coefficient (95% CI), *P*
Age (year)	−0.15 (−0.24– −0.06), 0.001	−0.35 (−0.5– −0.2), <0.001	−0.30 (−0.44– −0.17), <0.001	NR	NR
Sex (male/female)	NR	NR	NR	NR	NR
BMI (kg/m^2)	0.19 (0.07–0.3), 0.002	0.22 (0.02–0.41), 0.029	0.28 (0.1–0.46), 0.002	0.21 (0.05–0.36), 0.008	NR
Current smoking	NR	NR	NR	NR	NR
DM	−1.69 (−2.82– −0.55), 0.004	−3.12 (−4.99– −1.25), 0.001	−1.90 (−3.63– −0.16), 0.032	−1.52 (−3.02– −0.02), 0.048	NR
HTN	NR	NR	NR	NR	NR
HC	NR	NR	NR	NR	NR
Anemia	NR	NR	NR	NR	NR
History of stroke	NR	NR	NR	NR	−2.21 (−3.92– −0.5), 0.011
Cataract surgery	NR	NR	NR	NR	4.30 (2.99–5.6), <0.001
AL (mm)	−0.52 (–0.83– −0.22), 0.001	−1.43 (–2.01– −0.85), <0.001	−1.38 (−1.94– −0.82), <0.001	−0.73 (−1.21– −0.24), 0.003	NR
CCT (μm)	NR	NR	NR	NR	NR
Mean keratometry (diopter)	NR	NR	NR	NR	−0.65 (−0.99– −0.32), <0.001
IOP (mmHg)	NR	NR	NR	NR	NR

NR: Not retained in the final model (*P*>0.05), pRNFLT: Peripapillary retinal nerve fiber layer thickness, CI: Confidence interval, BMI: Body mass index, DM: Diabetes mellitus, HTN: Systemic hypertension, HC: Hypercholesterolemia, AL: Axial length, CCT: Central corneal thickness, IOP: Intraocular pressure

Table 6: The mean overall peripapillary retinal nerve fiber layer thickness (μ) in older adults according to the previous studies

First author	Country	Sample size (number of eyes)	Age (mean or range) years	Type of OCT	Mean overall pRNFLT
Arnould[20]	France	972	82.12	Spectralis (SD-OCT)	88.9
Lee[14]	South Korea	53	60–79	Cirrus (SD-OCT)	89.6
Rougier[13]	France	398	81.0	Spectralis (SD-OCT)	91.4
Sung[15]	USA	42	60–85	Stratus (TD-OCT)	93.4
Budenz[11]	USA	80	60–85	Stratus (TD-OCT)	60–69 years: 96.9 70–85 years: 94.1
Present study	Iran	2246	67.16	Spectralis (SD-OCT)	98.8
Xie[16]	China	91	>60	Topcon 3D OCT-2000 (SD-OCT)	60–69 years: 102.6 ≥70 years: 101.5
Manassakorn[17]	Thailand	30	>60	Stratus (TD-OCT)	102.4
Chen[21]	Taiwan	143	69.85	Stratus (TD-OCT)	102.8
Mansoori[18]	India	52	>60	OPKO/OTI (SD-OCT)	60–69 years: 113.1 ≥70 years: 110.0
Kanamori[19]	Japan	11	>70	Humphrey (TD-OCT)	114.0

pRNFLT: Peripapillary retinal nerve fiber layer thickness, OCT: Optical coherence tomography, SD: Spectral-domain, TD: Time-domain

As shown in Table 6, the mean overall pRNFLT in the elderly has been reported from 88.9 to 114.0 μ in the previous studies, with the mean found in the present study being in the middle of this range. Several factors can contribute to discrepancies, including differences in age range/mean, ethnicity, and type of OCT used.

The normative database of the Spectralis OCT is derived from 201 subjects of Caucasian origin enrolled in a patient registry with the following characteristics: 111 males, 90 females, mean age: 48.2 ± 14.5 years, age range: 18–78 years, without a history of glaucoma, normal IOP (<21 mmHg), normal visual field, and normal optic disc appearance.[30] Table 7 presents the part of the available published information from this database for comparison, which shows the 5th percentile of the overall and sectoral pRNFLT for the age 65 years.[30] Comparing these values with the 5th percentiles found in the present study at the same age [Table 3] shows significant differences, especially in the superior (87.4 vs. 94.2), inferior (87.1 vs. 102), and nasal (48.1 vs. 57) quadrants, so that the values of the present study are higher than the reference database. Therefore, due to the very low diagnostic threshold, the system database may interpret some pathological cases as normal in Iranian elderly at this age. One of the important limitations of the device database is the low sample size at older ages; it comprises only 13 people over 70 years old. Another weakness is the limitation of the device's database to the Caucasian ethnicity, while racial differences in pRNFLT have been reported.[10,11]

In the present study, the pRNFLT was the highest in the inferior quadrant, followed by the superior and nasal quadrants; the lowest pRNFLT was observed in the temporal quadrant. This finding indicates that the characteristic "double-hump" pattern of the pRNFL followed by the "inferior-superior-nasal-temporal" rule, previously reported by both OCT and histological studies mainly in younger populations,[31,32] also applies to the elderly population.

In line with most previous studies conducted in adult populations, we found a decrease in pRNFLT with advancing age. The phenomena of age-related degenerative loss of neurons in the inner retina have been well established using histologic analysis of retinal ganglion cells (RGCs) and their axons in the optic nerve.[33] Hence, an age-related decrease in pRNFLT is an expected finding. A point to consider is the difference in thinning rate which varies from 0.15 to 0.56 μ per year among different studies.[7,11,13,21,24,34] Age-related thinning rate of the overall pRNFLT in the present study (0.15 μ/per year) was similar to the studies with a wide age range (i.e., studies by Khawaja *et al*. [0.15 μ/per year][24] and Parikh *et al*. [0.16 μ/per year])[34] but less than studies performed specifically on the elderly (≥60 years) including studies by Rougier *et al*. (0.56 μ/per year)[13] and Chen *et al*. (0.49 μ/per year).[21] In addition to the age range, the degree of control over potential confounders can play a role in this variation. Many ocular or systemic factors affecting pRNFLT are related to age; therefore, not considering and controlling their effects in the multivariable model can increase the age coefficient or age-related pRNFL thinning rate. Moreover, the rate of pRNFLT decline with age may vary depending on ethnicity. In the present study, the age-related thinning was only evident in the thickest parts of the pRNFL (inferior and superior quadrants) while the nasal and temporal quadrants were not affected by age. A similar finding was found in previous studies on the elderly population.[13,21] It is not exactly clear why these two areas are most influenced by aging. However, this could be due to the fact that the atrophy process occurs more predominantly and rapidly in nerve fibers with larger diameters, and those fibers are more abundant in the vertical pRNFL quadrants.[35]

Table 7: The 5th percentile of overall and sectoral peripapillary retinal nerve fiber layer thickness (μ) in the Heidelberg Spectralis optical coherence tomography for the age 65 years[30]

	5th percentile
Overall	80.6
Superior sector*	87.4
Inferior sector*	87.1
Nasal sector	48.1
Temporal sector	52.0

*The superior and inferior sectors were not mentioned separately in the company's database report, rather they were indirectly calculated by averaging the superior-temporal and superior-nasal values (for the superior sector), as well as the inferior-temporal and inferior-nasal values (for the inferior sector)

The present study did not show a significant relationship between sex and pRNFLT. Although the overall and sectoral pRNFLTs in the inferior and nasal quadrants were significantly thicker in females, the relationship between sex and pRNFLT was not significant in the multivariable model after controlling the confounders. This finding clearly implies the role of confounding variables in this relationship. There are inconsistent reports regarding the association between sex and pRNFLT in the literature. Some studies, like the present study, did not find a significant relationship,[11,17,18,23] while others reported thicker pRNFLT in females and attributed it mainly to the protective effect of estrogen on the RNFL.[13,24] We believe that these controversies are mainly due to the difference in the degree of control over potential confounders, especially AL, which is shorter on average in women.

Increased AL was associated with a significant reduction in the overall pRNFLT as well as pRNFLT in all quadrants except the temporal quadrant; this finding was observed in the previous studies using both time-domain OCT and SD-OCT.[21,36,37] In general, there are two suggested mechanisms for the association between increased AL and reduced pRNFLT. First, elongation of the globe leads to mechanical stretching and thinning of the retina.[36] Second, axial elongation is associated with an increase in the diameter of the OCT scan circle projected onto the retina (magnification effect). The larger scan circle causes a larger distance from the optic nerve head (ONH) center.[38]

It has been shown that pRNFLT is negatively correlated with the distance from the ONH center in healthy individuals.[39] To investigate the second mechanism, some studies corrected for the magnification effect using the Littmann formula and reported that the significant correlation between AL and pRNFLT disappeared after magnification correction.[40,41] Lack of pRNFLT thinning in the temporal quadrant could be due to globe elongation dragging the retina toward the temporal horizon.[42]

The DM was associated with a reduced overall pRNFLT and pRNFLT in the superior, inferior, and nasal quadrants. The association between DM and pRNFLT has been associated with inconsistent results in the literature; some studies found no significant association[8,13] while others reported DM as a risk factor of RNFL thinning especially in the superior quadrant.[9,43-46] Various factors such as differences in sample size, the age distribution, DM diagnostic criteria, severity, and duration of DM can play a role in these discrepancies. Several mechanisms have been proposed for the impact of DM on the pRNFLT including apoptosis in RGCs, accumulation of advanced glycation end products in cribriform plates and around vessels in the optic nerve, impairment of retrograde axonal transport in large and medium-sized RGCs, and arterial blood flow insufficiency associated with diabetic microangiopathy.[46,47]

The BMI showed a statistically significant direct association with the overall pRNFLT and pRNFLT in all quadrants except the temporal quadrant. There are conflicting reports regarding the relationship between BMI and pRNFLT in the literature. Studies conducted on children and adolescents found an inverse relationship between these two parameters and suggested obesity as a risk factor for RNFL thinning at a young age.[48-50] On the other hand, studies with an older mean age found a direct association between BMI and pRNFLT;[8,51] this controversy indicates various BMI-related influencing mechanisms on pRNFL at different ages. Some possible mechanisms have been suggested for RNFL thinning with increasing BMI at younger ages, including a decrease in the endothelium vasodilator response mediated by nitric oxide and an increase in oxidative stress, excessive susceptibility of neuronal cells to oxidative stress caused by low-grade inflammation in obesity, and impairment of nutritional supply from the retinal and choroidal circulations resulting in a loss of ganglion cells and RNFL thinning.[48,50] At older ages, higher BMI is associated with increased intracranial pressure, and increased intracranial pressure can lead to optic disc edema due to optic disc vulnerability, making the measured RNFL thicker.[51]

The history of cataract surgery was associated with a significant increase in pRNFLT only in the temporal quadrant. Previous studies have also shown an increase in pRNFLT after cataract surgery,[52-54] although there are controversies regarding affected quadrants. This finding can be explained by the fact that cataracts interfere with signal transmission to the retina and its reflection from the retina; this influences the spatial delineation of the RNFL leading to enormous thinner measurements.[55] All types of cataracts can significantly affect the pRNFLT measurement using OCT with posterior subcapsular cataracts having the most impact.[56] The reason why the temporal quadrant was more affected by cataract surgery is probably that this quadrant is closer to the nodal point compared to other quadrants, so the central crystalline lens opacities could have a more pronounced impact on this quadrant.

A notable finding of the present study was the significant inverse relationship between a history of stroke and pRNFLT in the temporal quadrant. The previous case–control studies reported that the pRNFLT in patients with cerebral infarction was significantly lower compared to normal controls, and this finding was attributed to transneuronal retrograde degeneration.[57,58] This relationship was observed only in the temporal quadrant, probably because this quadrant anatomically has a thinner RNFL, which makes it more susceptible to damage and pRNFL thinning.

In conclusion, due to the population-based design and large sample size of the present study, its findings can be used as a reference database for pRNFLT in the elderly population. Older age, diabetes, and longer AL were associated with a decreased overall pRNFLT, while higher BMI was associated with an increased overall pRNFLT in the elderly. Some factors (such as history of stroke, history of cataract surgery, and mean k) did not affect overall pRNFLT; however, they were significantly related to pRNFLT in specific quadrants. Considering these factors is necessary for the correct clinical interpretation of pRNFLT to avoid misdiagnosis. It is recommended that OCT equipment manufacturers consider the ocular and systemic determinants of pRNFLT in their analysis algorithms.

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Conflicts of interest

There are no conflicts of interest.

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