• Clinical Research •

Structural-visual functional relationships detected by optical coherence tomography in varying age-cohorts' patients with optic neuritis

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Abstract

● **AIM:** To assess the relationships of final best-corrected visual acuity (BCVA) and the optic nerve structural loss in varying age-cohorts of optic neuritis (ON) patients.

● **METHODS:** This is a retrospective, cross-sectional study. Totally 130 ON subjects (200 eyes) without ON onset within 6mo were included, who underwent BCVA assessment, peripapillary retinal nerve fibre layer (pRNFL) and macular segmented layers evaluation by optical coherence tomography (OCT).

● **RESULTS:** For the 0-18y cohort, the final BCVA (logMAR) was significantly better and less frequent recurrences than adult cohorts (P=0.000). The final BCVA (logMAR) in all age-cohorts of the ON patients had negative and linear correlations to the pRNFL thicknesses and macular retinal ganglion cell layer (mRGCL) volumes, when the pRNFL thicknesses were reduced to the thresholds of 57.2-67.5 μm or 0.691-0.737 mm^3 in mRGCL volumes, respectively, with the strongest interdependence in the 19-40y cohort. The ON patients from varying age cohorts would be threatened by blindness when their pRNFL thicknesses dropped 36.7-48.3 μm or the mRGCL volumes dropped to 0.495-0.613 mm^3.

● **CONCLUSION:** The paediatric ON has best prognosis and young adult ON exhibits perfectly linear correlations of final vision and structural loss. The pRNFL and the mRGCL could be potential structural markers to predict the vision prognosis for varying-age ON patients.

● **KEYWORDS:** optic neuritis; age-cohort; final visual acuity; structural impairment; linear correlations
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INTRODUCTION

Optic neuritis (ON) is a variety of autoimmune-inflammatory demyelinating disease that exists as an isolated ON (ION) or an initial symptom of central neural system (CNS) demyelinating disease including multiple sclerosis (MS), neuromyelitis optica (NMO) or NMO spectrum disorders (NMOSD) and acute disseminated encephalomyelitis (ADEM), which is frequently involved in paediatric populations[1-5]. Most typical ON patients had a complete visual acuity (VA) recovery within 6mo after an episode of ON attack. The 89% pediatric ON and a little less of adult patients with ON had at least 20/40[6-7]. However, ON associated with MS, NMO or NMOSD and relapsing-remitting isolated syndrome would eventually cause blindness or disability after frequent relapsing-remitting of ON[2,7-8]. Previous studies demonstrated that 80% of the affected eyes from NMOSD patients and 38% of the eyes affected by MS experienced VA worse than 20/200 after an acute ON attack[2]. Whether the VA in the ON eyes recovered completely or not, their optic nerve microstructure always suffered irreversible impairments after an acute ON onset[9-10]. On the other hand, some ON patients exhibited rapid VA recovery to the baseline, others patients suffered permanent

visual loss after frequently ON attacks and their final VA eventually associated with structural loss in the afferent optic pathway when it decreased below a certain threshold. The quantified optic nerve microstructure loss could be a potential biomarker to predict the visual function prognosis, even they could reflect on of the quality of life for MS and NMOSD patients[8-14]. Additionally, age was another crucial factor for VA recovery in ON affected eyes, due to neural repairing or regenerative ability declining with aging[15-17]. Until now, there are few studies about quantified assessment correlations between final VA and structural loss in varying age patients with ON. Therefore, this study was to quantificationally assess the relationships of final best-corrected VA (BCVA) and the optic nerve structural loss detected by optical coherent tomography (OCT) in varying age-cohorts of ON patients and analysed the thresholds of optic nerve loss to predict final VA.

SUBJECTS AND METHODS

Ethical Approval This age-cohort study was conducted at the Chinese People's Liberation Army General Hospital with approval of their Institutional Ethics Committee (NO.2017MBD-019). The study adhered to the tenets of the Helsinki Declaration. The written informed consents were obtained from all subjects or their guardians and were kept in Chinese People's Liberation Army General Hospital and Beijng Children's Hospital, Capital Medical University.

Study Design This was a retrospective, cross-sectional study.

Participants Consecutive ON patients who had been diagnosed according to the criteria from the Optic Neuritis Treatment Trials (ONTT)[7] and had MRI images to excluded other CNS diseases from the Department of Ophthalmology Beijing Children's Hospital, Capital Medical University and the Chinese Liberation Army General Hospital, from July 2014 to December 2019, were recruited as participants. The staff and their children from the two hospitals served as healthy controls (HCs). All ON patients were divided into 3 cohorts based on age: 0-18y, 19-40y and 41-70y.

Inclusion Criteria Patients diagnosed with ON without ON recurrence within 6mo and their OCT images should met the OSCAR-IB which is the international quality control criteria for retinal OCT[18] and images quality were good enough to perform retinal segmented analysis and correctly centred in circular scans. The HCs participants whose BCVA was equal to or better than 0.8 (40/50).

Exclusion Criteria Participants who had a refractive error of more than ±6.00 spherical degree, ±2.00 cylindrical degree or an intraocular pressure value of more than 21 mm Hg were excluded. Participants with ocular diseases and surgery history, and with systemic nervous diseases caused by other than inflammation demyelination disorders identified by a senior neurologist were also excluded.

Ophthalmological Examinations All participants underwent slit-lamp microscope and indirect-ophthalmoscopy examinations by two senior ophthalmologists.

Visual Function Evaluation All the ON participants had their BCVA monocularly evaluated with the Snellen visual chart, and the BCVA values were converted to the logarithm values of the minimum angle of resolution (logMAR). Among them, the counting fingers (CF) and hand motion were identified as logMAR 1.85 and logMAR 2.00, respectively, with light perception and no light perception as logMAR 2.70 and logMAR 3.00, respectively[19]. The ON patients who were better than 0.1 with BCVA and whose age was more than 7 years also had visual field tests.

Optical Coherent Tomography Examinations Both ON patients and HCs had a peripapillary retinal nerve fibre layer (pRNFL) and inner macular segmented layers assessment with Spectralis-OCT (Heidelberg Engineering Corporation, Heidelberg, Germany) and Microsoft 6.0.9 Nisite (Heidelberg Engineering Corporation, Heidelberg, Germany) according to standard operational protocols on the same day as the other ophthalmological examinations[20-21]. All the participants underwent OCT examinations in room light conditions and they did not have pupil dilation before the OCT performances. The pRNFL assessment used a 3.4 mm circle A-scanning centre on an optic disc. To better visualise retinal structure and precisely measure in repeated examinations multiple times [Automatic Real-Time (ART)=100] and eye-track models were performed. The global pRNFL thicknesses were assessed. The B-scanning model was used to measure the macular segmented layers and automatically calculate the total volumes of each layer within the outer circle zone (6-mm diameter circle) mapped by the Early Treatment Diabetic Retinopathy Study (ETDRS) by Microsoft 6.0.9 Nisite, which mainly comprised the macular retinal nerve fibre layer (mRNFL), macular retinal ganglion cells layer (mRGCL), macular inner plexiform layer (mIPL) and macular inner nuclear layer (mINL). The OCT images obtained with a signal strength less than 15 were discarded according to OSCAR-IB quality control criteria[18,20-21]. Two experienced technicians who were blind to the participants' clinical information performed all the OCT examinations.

Statistical Analysis All the data were analysed by SPSS.19.0 (IBM, USA), and graphic plots were performed using GraphPad Prism 5 (GraphPad Software, USA). The average measurements of OCT and BCVA were expressed by mean and standard deviation, whereas the average age of the participants was displayed by median and interquartile range (IQR). The comparisons of the age and gender in the various cohorts were tested by the Mann-Whitney *U* test and Pearson's Chi-square test, respectively. The BCVA in the various age-cohorts was analysed by analysis of variance (ANOVA). The

OCT measurements in the various cohorts were tested by multivariate linear regression models and Bonferroni-Holm tests with eye gender (right eye or left eye) and ON episodes as covariant. The Pearson's test for linear regression was performed to evaluate the correlations of the BCVA and the retinal structural alterations detected by OCT. The statistical significance was set when the *P* value was less than 0.05.

RESULTS

Among the 300 patients (487 eyes) with ON who were recruited and underwent assessment in this study, 130 ON patients (200 eyes) who met the included criteria participated in the study. The 130 ON patients were grouped into three cohorts based on age (Figure 1). In the age-cohorts, the gender and age compositions were strictly matched to their HC cohorts. Most of the included patients with ON suffered more than one episodes of ON attacks and the average episodes of ON onset and other clinical and demographic features are shown in Table 1. The final BCVA in 0-18y cohort (logMAR: 0.16±0.39) was best followed by the 41-70 (logMAR: 1.14±1.22) and 19-40y (logMAR: 1.19±1.08) cohorts (Figure 2A). As for the ON episodes, both the 19-40 and the 41-70y cohorts were more frequent than those of the 0-18y cohort (Figure 2B). In contrast to the global pRNFL thicknesses in the HCs, all the ON patients exhibited severe thinning in the pRNFL after the ON attacks (all *P*=0.000). The eyes from 19-40y cohort lost the most, approximately 54.5 μm; then, the 41-70y cohort lost by 50.1 μm, followed by the 0-18y cohort with 34.7 μm (Table 2). In comparisons within the ON patients, the global pRNFL thicknesses of the 0-18y cohort were reduced less than that of both the 19-40 and the 41-70y cohorts (*P*=0.02, 0.01); there were no significant differences between the latter age-cohorts (*P*=1.000; Figure 3).

Final BCVA in the ON affected eyes from all the age-cohorts of the patients was related positively to the pRNFL thicknesses and the volumes of mRNFL, mRGCL, and mIPL (Figure 4). Of those, the linear relationships of the pRFNL thicknesses and the mRGCL volumes to the final BCVA were much stronger in varying age cohorts, when the pRNFL thicknesses were reduced to the thresholds of 57.2-67.5 μm or 0.691-0.737 mm^3 in mRGCL volumes, respectively, and 19-40y cohort had the strongest correlations. The thresholds of pRNFL and mRGCL loss after ON attacks to predict the variety of final visual loss, ranging from normal to CF, were listed in Table 3. When the pRNFL thicknesses and the mRGCL volumes decreased to 57.2-67.5 μm and 0.691-0.790 mm^3, respectively, the ON patients suffered irreversible visual loss and dropped close to 36.7-48.3 μm and 0.495-0.613 mm^3, respectively, predicting of blindness in law.

DISCUSSION

The neural structural impairments that emerged from non-infectious inflammatory demyelination or astrocytopathy and subsequent neuro-degeneration were not independent of the corresponding functional injuries. The cerebral lesion patterns measured by MRI were associated with the disability progression in MS and NMO[22-23]. However, it was impossible to evaluate their correlations accurately due to the limitations of the measurement technique. However, optic nerve can be precisely quantified by OCT with a 3.5 μm axial resolution[24], and the visual function can be evaluated readily and quantitatively. Previous studies demonstrated that optic nerve alterations correlated to final visual acuity in ON patients; furthermore, they reflect the cerebral structural alterations in

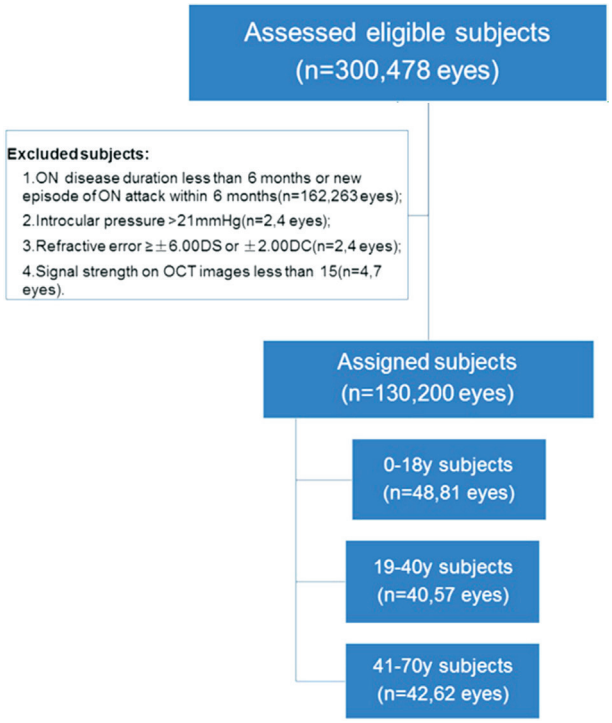

Figure 1 Flowchart of the participants and the age-cohorts of the patients with optic neuritis ON: Optic neuritis; OCT: Optical coherence tomography.

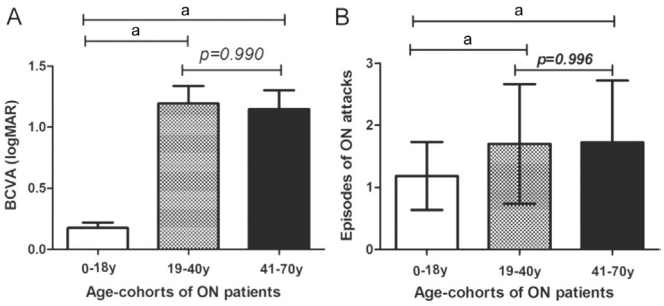

Figure 2 Final BCVA (logMAR) eyes affected by ON and the number of episodes of ON onsets in varying age-cohorts A: The final VA in eyes affected by ON from the 0-18y cohort was much better than that of the 19-40y and the 41-70y cohorts. The episodes of ON onsets in the 0-18y ON cohort were less than those of the 19-40y and the 41-70y cohorts. BCVA: Best-corrected visual acuity; ON: Optic neuritis; VA: Visual acuity. [a]*P*<0.01.

Table 1 Demographic and clinical features of subjects in the age-cohort study

Clinical features	ON	HCs	*P*
0-18y (*n*)	48 (81 eyes)	58 (115 eyes)	-
Age (y), median (IQR)	10.0 (8.0-13.0)	10.0 (9.0-12.0)	0.747[a]
Gender (M/F)	26/22	36/22	0.411[b]
BCVA (logMAR), mean±SD	0.16±0.39	-	-
Episodes, mean±SD	1.19±0.55	-	-
Disease duration (mo), median (IQR)	11.0 (7.0-34.0)	-	-
19-40y (*n*)	40 (57 eyes)	37 (74 eyes)	-
Age (y), median (IQR)	39.0 (27.8-48.5)	28 (25.0-34.0)	0.577[a]
Gender (M/F)	9/31	9/28	0.791
BCVA (logMAR), mean±SD	1.19±1.08	-	-
Episodes, mean±SD	1.70±0.96	-	-
Disease duration (mo), median (IQR)	19.0 (8.0-60.0)	-	-
41-70y (*n*)	42 (62 eyes)	15 (30 eyes)	-
Age (y), median (IQR)	30.0 (26.5-51.5)	45 (43.0-57.0)	0.064[a]
Gender (M/F)	12/30	10/15	0.335[b]
BCVA (logMAR), mean±SD	1.14±1.22	-	-
Episodes, mean±SD	1.74±1.00	-	-
Disease duration (mo), median (IQR)	24.0 (12.0-72.0)		
Total subjects	130 (200 eyes)	-	-

ON: Optic neuritis; HCs: Healthy controls; IQR: Interquartile range; M/F: The ratio of male to female; SD: Standard deviation. [a]Mann-Whitney *U* test; [b]Pearson's test of Chi-square tests.

Table 2 Results of pRNFL thicknesses and inner macular segmented layer volumes in age-cohort patients with ON compared with their HCs respectively

mean±SD

Items	ON	HCs	d-value (ON-HCs)	*P*[a] (MD, SE)
Global pRNFL (μm)				
0-18y	65.9±17.8	100.6±8.8	-34.7	0.000 (-34.72, 1.99)
19-40y	52.7±22.8	107.2±8.5	-54.5	0.000 (-54.52, 2.92)
41-70y	51.7±15.3	101.8±11.9	-50.1	0.000 (-50.19, 3.20)
mRNFL volume (mm^3)				
0-18y	0.550±0.137	0.840±0.111	-0.29	0.000 (-0.29, 0.02)
19-40y	0.490±0.162	0.844±0.131	-0.354	0.000 (-0.36, 0.03)
41-70y	0.512±0.112	0.821±0.972	-0.309	0.000 (-0.31, 0.02)
mRGCL volume (mm^3)				
0-18y	0.768±0.146	1.116±0.077	-0.348	0.000 (-0.35, 0.017)
19-40y	0.656±0.140	1.145±0.107	-0.489	0.000 (-0.49, 0.02)
41-70y	0.633±0.149	1.141±0.733	-0.508	0.000 (-0.51, 0.03)
mIPL volume (mm^3)				
0-18y	0.690±0.091	0.901±0.491	-0.211	0.000 (-0.21, 0.01)
19-40y	0.647±0.082	0.932±0.068	-0.285	0.000 (-0.28, 0.01)
41-70y	0.654±0.752	0.925±0.444	-0.271	0.000 (-0.27, 0.02)
mINL volume (mm^3)				
0-18y	1.079±0.080	1.042±0.639	0.037	0.001 (0.04, 0.01)
19-40y	1.105±0.162	1.029±0.063	0.076	0.000 (0.08, 0.02)
41-70y	1.107±0.109	1.070±0.614	0.037	0.090 (0.04, 0.02)

ON: Optic neuritis; HCs: Healthy controls; d-value: Different value; pRNFL: Peripapillary retinal nerve fiber layer; mRNFL: Macular retinal nerve fiber layer; mRGCL: Macular ganglion cells layer; mIPL: Macular inner plexiform layer; mINL: Macular inner nuclear layer; SD: Standard deviation; MD: Mean differences; SE: Standard error. [a]Multivariate linear regression models and Bonferroni tests.

MS patients[9-11,22-23]. However, few of them considered the age influence. In this study, we studied structural-final visual functional relationships in varying age-cohort ON patients and outcomes revealed that paediatric ON patients had the

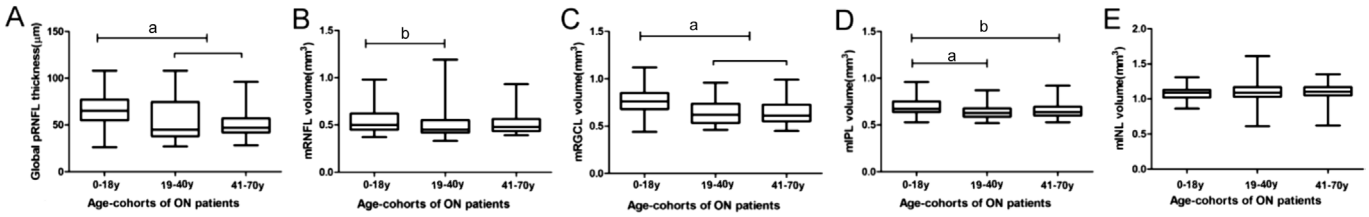

Figure 3 pRNFL thicknesses and macular segmented layer volume alterations in age varying ON cohorts A: Global pRNFL thicknesses in eyes affected by ON from the 0-18y cohort lost less than that of the 19-40y and the 41-70y cohorts; B: The mRNFL volumes in eyes affected by ON from the 0-18y cohort had a milder decrease than that of the 19-40y cohort; C: The mRGCL volumes in eyes affected by ON from the 0-18y cohort lost less than the other cohorts; D: The mIPL volumes in the eyes affected by ON from the 0-18y cohort lost less than the other cohorts; E: The mINL volumes went up with increased age; however, there were no significant differences in the three cohorts of ON patients. pRNFL: Prepapillary retinal nerve fibre layer; ON: Optic neuritis; mRNFL: Macular retinal nerve fibre layer; mRGCL: Macular retinal ganglion cell layer; mIPL: Macular inner plexiform layer; mINL: Macular inner nuclear layer. $^{a}P<0.01$, $^{b}P<0.05$.

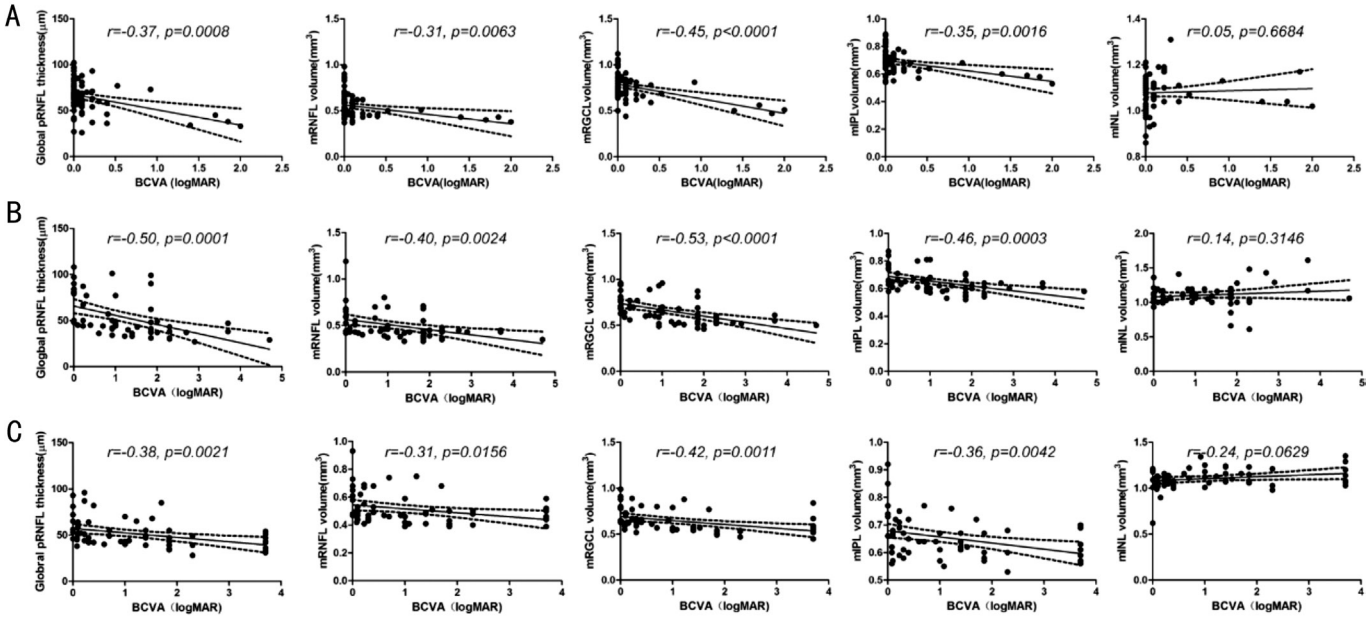

Figure 4 Correlations between the final BCVA and pRNFL thicknesses and the macular segmented layer volumes in eyes affected by ON from the varying age-cohorts The pRNFL thicknesses and all of the inner macular segmented layers volumes, except for the INL, were all negatively and linearly related to the final BCVA in the ON affected eyes from the 0-18y cohorts (A), the 19-40y cohorts (B) and the 41-70y cohorts (C). The pRNFL thicknesses and the RGCL volumes had stronger relations to the final BCVA, as compared with the mRNFL and the mIPL. Among them, the structural-functional linear correlations in the eyes affected by ON from the 19-40y cohort were more perfect than those of the other age-cohorts. BCVA: Best-corrected visual acuity; pRNFL: Prepapillary retinal nerve fibre layer; ON: Optic neuritis; mRNFL: Macular retinal nerve fibre layer; mRGCL: Macular retinal ganglion cell layer; mIPL: Macular inner plexiform layer; mINL: Macular inner nuclear layer.

best prognosis and young adult ON patients exhibited perfectly linear correlations of final vision and structural loss. The pRNFL and the mRGCL could be potential structural markers to predict the vision prognosis for varying-age ON patients. Paediatric ON had much better final visual acuity and less episodes of ON onsets than the adult ON. Consistent with that finding, the paediatric ON cohorts had a better prognosis with excellent visual recovery and a lower risk of recurrence, even though they presented severely vision decreasing at the initial onset of ON[25].

Previous studies verified that the risk of ON relapsing and developing to MS became higher with the increased age of the ON presentation. To some extent, this outcome was similar to the opinion of fewer frequencies of ON in younger patients[26-28]. Additionally, the gender predilection of the paediatric ON was equal with the 26:22 of the ratio of female to male, whereas the female frequencies were much higher in the adult ON, with an approximate 3-2:1 ratio of female to male, which was compatible with the distinct features of paediatric as compared to adult ON[1,27]. These distinguishing characteristics between paediatric and adult ON could attribute to their distinct pathogenesis. Paediatric ON usually occurs as a post-infection of a virus, a vaccination or ADEM and its

Table 3 The correlations of global pRNFL thicknesses and mRGCL volumes in age-cohort ON patients, with their BCVA (logMAR), and their OCT measurements' cut-off values for various-level visual losses 95%CI (best-fit values)

Items	0/20/20	0.301/20/40	0.523/20/60	1/20/200	1.85/CF	*r, P*
Global pRNFL thickness (μm)						
0-18y	63.5-71.6 (67.5)	58.5-66.5 (62.5)	54.8-62.9 (58.8)	46.8-54.9 (50.9)	32.8-40.9 (36.7)	-0.37, 0.0008
19-40y	57.9-73.3 (65.6)	54.9-70.3 (62.6)	60.3-68.1 (60.4)	47.4-63.4 (55.7)	39.5-54.9 (47.2)	-0.50, 0.0001
41-70y	52.3-62.2 (57.2)	50.8-60.7 (55.8)	49.8-59.7 (54.7)	47.5-57.4 (52.4)	43.4-53.3 (48.3)	-0.38, 0.0021
mRGCL volume (mm^3)						
0-18y	0.750-0.821 (0.790)	0.710-0.773 (0.742)	0.675-0.738 (0.707)	0.599-0.662 (0.631)	0.464-0.527 (0.495)	-0.45, <0.0001
19-40y	0.689-0.785 (0.737)	0.669-0.765 (0.717)	0.654-0.750 (0.702)	0.621-0.717 (0.669)	0.563-0.659 (0.611)	-0.53, <0.0001
41-70y	0.650-0.731 (0.691)	0.637-0.718 (0.678)	0.628-0.709 (0.669)	0.608-0.689 (0.649)	0.572-0.653 (0.613)	-0.42, 0.0011

BCVA: Best corrected visual acuity; pRNFL: Peripapillary retinal nerve fiber layer; mRGCL: Macular retinal ganglion cell layer; CF: Counting fingers; ON: Optic neuritis; OCT: Optical coherence tomography; CI: Confidence interval; Best-fit values: Cut-off values were calculated by linear regression equation; *r* value and *P* value obtained from linear regression test.

demyelination processes were stimulated by the virus, which is considered as a distinct entity from adult ON. Both paediatric ON and ADEM are typically a monophasic process with the same age of presentation and a better prognosis than that of MS, NMO and NMOSD[27,29-30].

As revealed by this study, due to the number and functional decline of the neural stem cells, the retinal structure impairment of ON worsens with increased age[16,31]. The pRNFL thicknesses and mRGCL volumes lost less in the paediatric ON, followed by the 19-40y, and more than with the 40y of adult ON. Aside from the distinct pathogenesis between paediatric and adult ON, this could be explained by the much stronger neural repairing and regenerating capability to preserve retinal microstructures and restore visual function in the youth, as compared to older populations. Moreover, the pRNFL and mRGCL thinning was also associated with the final visual acuity in varying age-cohorts of ON, which were in accordance with previous studies[9,11,13]. Final visual acuity was related linearly and negatively to the pRNFL thicknesses and mRGCL volumes in varying age ON patients when they were reduced to the thresholds of 57.2-67.5 μm and 0.691-0.790 mm^3 in pRNFL thicknesses and mRGCL volumes, respectively. When pRNFL thicknesses or the mRGCL volumes were reduced close to 36.7-48.3 μm and 0.495-0.613 mm^3 in both eyes after frequent ON attacks, it warned doctors to prevent next ON attack as possible as they can. Otherwise, the patients would be likely to become a blind. Additionally, linear interdependency was strongest in young adult ON patients and the possible reasons could be the more suitable repair and regeneration of the optic nerve to the demyelinating injury in young adult ON patients, rather than strong repairs in paediatric ON and under repairs in aged ON patients[16,30].

Regardless of the useful parameters for predicting the vision prognosis drawn by this study, there are some limitations. This was a retrospective and cross-sectional study, and the biases of the participants recruited and the small size of the sample will weaken the reliability of the conclusions. In addition, the disease durations, the number of episodes of ON and the treatments were not well matched in the various cohorts, which also leads to bias in the outcomes. Moreover, the correlations of the structure-function for ON eyes affected by gender, types of ON, population and races[9,13,30], which were not considered in this study.

In conclusion, in this study, paediatric ON patients had the best prognosis and young adult ON patients exhibited perfectly linear correlations of final vision and structural loss. The final BCVA exhibited irreversible loss when the pRNFL thicknesses were reduced to 57.2-67.5 μm or mRGCL volumes dropped to 0.691-0.737 mm^3, respectively and would be threatened by blindness when the pRNFL thicknesses dropped 36.7-48.3 μm or the mRGCL volumes dropped to 0.495-0.613 mm^3. These structural biomarkers could be potential cues to guide the treatment programme for ON patients.

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