General Psychiatry

Association between retinal layer thickness and postoperative delirium in older patients

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To cite: Shi Z, Ma X, Tang T, *et al*. Association between retinal layer thickness and postoperative delirium in older patients. *General Psychiatry* 2025;**38**:e101740. doi:10.1136/gpsych-2024-101740

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gpsych-2024-101740).

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Received 05 June 2024
Accepted 09 January 2025

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ABSTRACT

Background Postoperative delirium is one of the most common complications in the older surgical population, but its pathogenesis and biomarkers are largely undetermined. Retinal layer thickness has been demonstrated to be associated with cognitive function in mild cognitive impairment and patients with Alzheimer's disease. However, relatively little is known about possible retinal layer thickness among patients with postoperative delirium.

Aims We aimed to investigate the relationship between retinal layer thickness and postoperative delirium in this cross-sectional study.

Methods The participants (≥65 years old) having elective surgery under general anaesthesia were screened via medical records from Shanghai 10th People's Hospital. Preoperative macular thickness and peripapillary retinal nerve fibre layer (RNFL) thickness were measured using optical coherence tomography (OCT). The Confusion Assessment Method (CAM) algorithm and CAM-Severity (CAM-S) were used to assess the incidence and severity of postoperative delirium on the first, second and third days after surgery.

Results Among 169 participants (mean (standard deviation (SD) 71.15 (4.36) years), 40 (24%) developed postoperative delirium. Notably, individuals who developed postoperative delirium exhibited thicker preoperative macular thickness in the right eye compared with those who did not (mean (SD) 283.35 (27.97) µm vs 273.84 (20.14) µm, p=0.013). Furthermore, the thicker preoperative macular thickness of the right eye was associated with a higher incidence of postoperative delirium (adjusted odds ratio 1.593, 95% confidence interval (CI) 1.093 to 2.322, p=0.015) and greater severity (adjusted mean difference (β)=0.256, 95% CI 0.037 to 0.476, p=0.022) after adjustment for age, sex and Mini-Mental State Examination (MMSE) scores. However, such a difference or association did not appear in the left macular or bilateral peripapillary RNFL thicknesses.

Conclusions Current findings demonstrated that preoperative macular thickness might serve as a potential non-invasive marker for the vulnerability of developing postoperative delirium in older surgical patients. Further large-scale validation studies should be performed to confirm these results.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Postoperative delirium is one of the most common complications in the older surgical population, causing an increased risk of developing dementia. Retinal layer thickness has been demonstrated to be associated with cognitive conversion, but retinal layer thickness in patients with postoperative delirium remains unclear.

WHAT THIS STUDY ADDS

⇒ Macular thickness in the right eye was positively associated with the incidence and severity of postoperative delirium in older surgical patients under general anaesthesia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings demonstrated that macular thickness might be a novel, non-invasive and convenient marker for predicting the vulnerability of developing postoperative delirium.

INTRODUCTION

Postoperative delirium is one of the most common postoperative complications in older patients, associated with prolonged hospital stays, higher discharge rates to nursing homes, and a more significant decline in activities of daily living (ADL), as well as increased morbidity and mortality.[1 2] The annual healthcare costs attributable to postoperative delirium are approximately $32.9 billion in the United States. Despite its poor outcomes and high costs, the biomarkers and pathogenesis of postoperative delirium remain largely undetermined. This knowledge gap is a barrier that impedes further studies, particularly in developing new diagnostic strategies, identifying patients at increased risk, and developing new interventions for postoperative delirium. Numerous studies have indicated that patients who experienced postoperative delirium would have an increased risk of developing cognitive decline or dementia compared with those who did not.[3] Delirium has been considered to represent a modifiable risk factor for dementia and thus provides an important interventive

window for reducing cognitive impairment.[4] Therefore, establishing biomarkers to identify individuals at high vulnerability of developing postoperative delirium would be a significant contribution.

Previous studies have shown that inflammation,[5] Alzheimer's disease neuropathogenesis such as β-amyloid 42 (Aβ42) levels in cerebrospinal fluid (CSF),[6] and increased plasma phosphorylated τ and neurofilament light were associated with the development of postoperative delirium.[7] However, establishing non-invasive and inexpensive biomarkers and further identifying the pathogenesis of postoperative delirium remain largely to be determined.

Visual impairment has been recognised as an independent risk factor for developing postoperative delirium.[8] The retina, which plays the most critical role in maintaining visual function, has long been a promising target for developing novel, cost-effective and accessible biomarkers for investigating central nervous system disorders. This is made possible through optical coherence tomography (OCT), an advanced imaging technique known for its high-resolution and non-invasive nature. Specifically, retinal layer thickness measured by OCT has been demonstrated to be associated with cognitive function in patients with Alzheimer's disease (AD), and retinal degeneration is frequently recommended as an early target for AD biomarkers.[9] Population-based studies have corroborated this by revealing a correlation between a thinner retinal nerve fibre layer (RNFL) and baseline cognitive dysfunction, as well as future cognitive decline over time.[10] Delirium and dementia have shared biomarkers, but whether macular thickness or peripapillary RNFL thickness measured by using OCT measures could predict the vulnerability of developing postoperative delirium among the non-demented surgical population has not been determined.

Therefore, this study aimed to evaluate the relationship between retinal layer thickness and postoperative delirium. We hypothesised that preoperative macular thickness or peripapillary RNFL thickness was associated with the incidence and severity of postoperative delirium.

METHODS

This cross-sectional study is of older patients undergoing elective surgeries under general anaesthesia. All participants provided written informed consent for the study. The results in the manuscript were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Study population

Patients scheduled for elective orthopaedic surgery (eg, knee/hip replacement surgeries or discectomy) or urological surgery (eg, transurethral endoscopic lithotripsy and transurethral resection of the prostate) at Shanghai 10th People's Hospital were screened from June 2018 to May 2020. Participants were included if they met the following eligibility criteria: (1) aged 65 years or older; (2) scheduled for surgery under general anaesthesia; (3) hearing, vision and communication capability and thus able to provide informed consent; and (4) native language is Chinese Mandarin. Participants were excluded if they had (1) pre-existing dementia at the time of enrollment, as evidenced by a score below an education-adjusted threshold (18 for illiterate individuals, 20 for those with 1–6 years of education, or 24 for those with ≥7 years of education) on the Chinese version of the Mini-Mental State Examination (MMSE)[11]; (2) preoperative delirium screened by the Confusion Assessment Method (CAM) algorithm[12]; (3) prior neurologic diseases, for example, Parkinson's disease, multiple sclerosis or stroke according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10); (4) a history of mental disorders, for example, major depressive disorder or schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); (5) known diseases contributing to retinal pathologies, for example, diabetes, glaucoma, cataracts, macular degeneration or intraocular pressure (IOP) greater than 24 mm Hg; (6) a history of hypertension leading to hypertensive retinopathy; or (7) presently participating in other research.

Preoperative assessment

After the patients were admitted to the hospital, two well-trained researchers performed preoperative in-person assessments the day before the scheduled surgery by following a standard protocol. Characteristics of the participants were collected, including age, sex, education and body mass index (BMI). Moreover, the age-adjusted Charlson Comorbidity Index (CCI) was obtained through patient interviews or medical records based on the validated Charlson comorbidity coding algorithms, with higher scores indicating more comorbidities.[13] Additionally, IOP measurements of the bilateral eyes were performed for all participants. The CAM algorithm was performed preoperatively to exclude preoperative delirium. The Chinese version of the MMSE (score ranges from 0 to 30, with a higher score indicating better cognitive function) was used to exclude pre-existing dementia with education-specified cut-off values. This instrument has shown good validity and reliability in dementia screening among older Chinese populations.[11]

Optical coherence tomography (OCT) examination

Retina imaging was conducted on the same day as the preoperative assessments. The same technologist performed all OCT examinations according to a standard protocol, and a board-certified ophthalmologist reviewed all the OCT images to ensure the exclusion of participants with retinal pathologies or poor-quality OCT images. Specifically, default Macular Cube 512×128 scan and Optic Disc Cube 200×200 protocols were used to determine macular thickness and peripapillary RNFL thickness, respectively. Moreover, the macular ganglion

cell-inner plexiform layer (mGC-IPL) thickness was also measured by a Ganglion Cell OU Analysis, which generated the thickness of the mGC-IPL in the 6 mm by 6 mm cube and the elliptical annulus centred on the fovea. The mean mGC-IPL thicknesses of the bilateral eyes were provided by the software. All measurements were obtained using Spectral Domain OCT (ZEISS Cirrus HD-OCT 5000 OCT, Carl Zeiss Meditec, Dublin, CA, USA; software version 6.5). A scan was saved only if the fundus image was sufficiently visible to distinguish the region of interest and the scanning circle. Images with eye movements during scans, poor centration, poor focus, low analysis confidence, or signal strength less than 4/10 were excluded. All scans were repeated three times per eye, and the average of these measurements was taken for both eyes.

Anaesthesia and surgery

All participants were scheduled for orthopaedic or urological surgery under standardised perioperative care. The anaesthesia was induced with propofol (2 mg/kg), sufentanil (0.5–1 µg/kg) and cisatracurium (0.5 mg/kg) and maintained with anaesthetic sevoflurane (0.5 mL/kg) and propofol (5 mg/kg). In addition, information regarding the American Society of Anesthesiologists (ASA) classification of physiological status, surgery type, and length of anaesthesia administration and operation was obtained by reviewing the patient's anaesthesia records.

Postoperative delirium assessment

The primary outcome was the incidence of postoperative delirium within three postoperative days. Each participant was assessed twice daily at 10:00 (morning) and 16:00 (afternoon) according to the CAM diagnostic algorithm. The CAM algorithm consists of four clinical criteria: (1) acute onset or fluctuating course of mental status, (2) inattention, (3) disorganised thinking, and (4) altered level of consciousness. To diagnose delirium, both the first and the second criteria must be present, and either the third or the fourth criteria must be present. Participants were defined as having postoperative delirium if there was at least one positive delirium assessment of CAM on any of the postoperative three days.

The secondary outcome was the severity of postoperative delirium, quantified by using the CAM-Severity (CAM-S) long-form, which comprises severity ratings for 10 delirium features (range from 0 to 19), including the four diagnostic features listed above and six additional features (disorientation, memory impairment, psychomotor retardation, psychomotor agitation, perceptual disturbances, and sleep–wake cycle disturbance). The CAM-S has good reliability and validity among older Chinese adults; the CAM-S scores obtained from postoperative days one, two and three were averaged for analysis.[14]

Statistical analysis

Since there were no studies that had explored OCT-determined retinal layer thickness in participants with postoperative delirium, the estimation of sample size was calculated according to a study which compared macular thickness between healthy participants and patients with mild cognitive impairment (MCI), with respective results of 208.66 (24.70) µm versus 228.19 (24.63) µm.[15] As with previous studies, we estimated the incidence of postoperative delirium to be above 20% in the older surgical population.[14] We determined that 140 participants (28 participants in the delirium group and 112 participants in the non-delirium group) would be required to detect a significant difference in macular thickness between participants with and without postoperative delirium at a significance level of 5% and a power of 95%. We expected a dropout rate of 20% and thus planned to enrol at least 175 participants. Ultimately, 200 participants were enrolled, and 169 were included in the final data analysis.

The Kolmogorov-Smirnov test was used to test the normality of all variables. The between-group differences were compared using independent Student's t-test (mean (standard deviation (SD))) or Mann-Whitney U test (median (interquartile range (IQR))) for continuous variables, and χ^2 test or Fisher's exact test for categorical variables (n (%)). The differences in retinal layer thickness between the participants who developed postoperative delirium and those who did not were initially compared. Univariate and multivariable logistic regressions were employed to assess the association between retinal layer thickness and the incidence of postoperative delirium. The retinal layer thickness was scaled with Z scores in all the models, and results were presented as odds ratio (OR) per SD change of retinal layer thickness with 95% confidence interval (CI). Generalised linear regression was used to assess the association between retinal layer thickness and the severity of postoperative delirium, and results were presented as a mean difference (β coefficient) per SD change in the retinal layer thickness with 95% CI. All the models were applied before and after adjustment for age, sex and preoperative MMSE due to their clinical relevance and previously defined relationships with postoperative delirium. Assumptions for linearity and model fit were considered by examining the residuals and the calibration curves to ensure the models adequately fit the data. R (version 4.0.5, Vienna, Austria) was used to analyse the data, with p-values less than 0.05 as the significance level.

RESULTS

Participant characteristics

The study flowchart in figure 1 shows the enrolment, exclusions and patients available for final data analysis. A total of 263 patients were preliminarily screened for eligibility, and 63 were excluded because they declined participation (n=53) or were participating in another clinical study (n=10). Of the enrolled 200 participants,

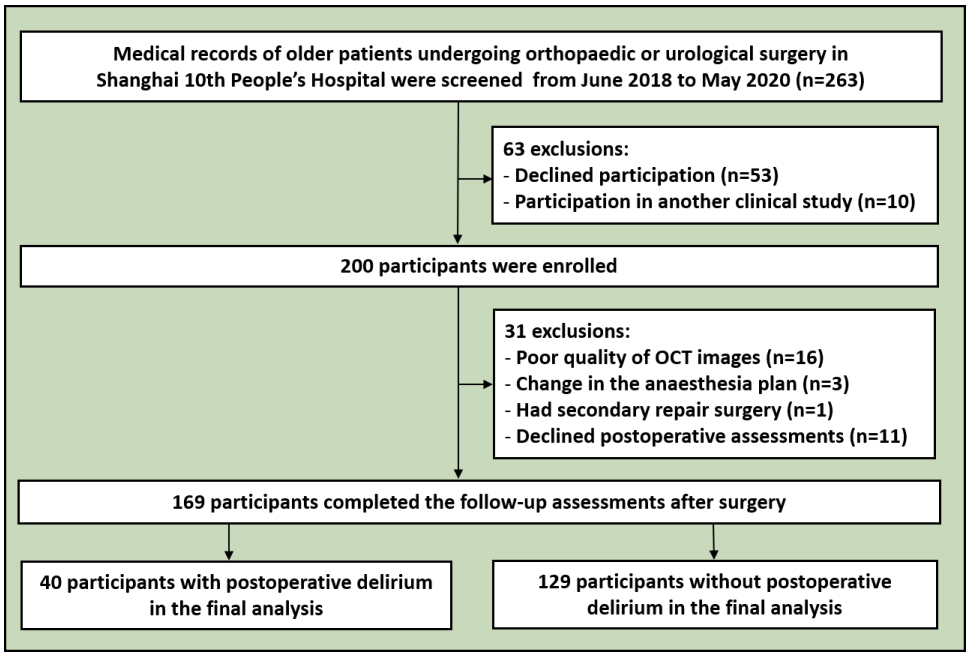

Figure 1 The study flowchart shows the enrolment, exclusions and participants available for analysis. OCT, optical coherence tomography.

31 were further excluded due to the poor quality of their OCT images (n=16), change in the anaesthesia plan (n=3), the inclusion of secondary repair surgery (n=1), or their declining postoperative assessments (n=11). Ultimately, 169 participants (mean (SD) 71.15 (4.36) years, 57% female) were included in the data analysis. Additionally, there were no significant differences in age, sex, IOP, macular thickness, peripapillary RNFL thickness or mGC-IPL thickness of the bilateral eyes between the participants who were included in the study (n=169) and those who dropped out (n=31) (see online supplemental table 1).

Among the 169 participants, 40 (24%) developed postoperative delirium. Noteworthy, the participants who developed postoperative delirium had lower preoperative MMSE scores than those who did not (median (IQR): 25.00 (24.00–27.00) vs 27.00 (25.50–28.00), p<0.001). There were no statistically significant differences in other characteristics between participants with and without postoperative delirium (see table 1).

Greater macular thickness in participants with postoperative delirium

We then compared the macular thickness, peripapillary RNFL thickness and mGC-IPL thickness of the bilateral eyes between the participants who developed postoperative delirium and those who did not. The data showed that participants with postoperative delirium had greater preoperative macular thickness of the right eye compared with those without postoperative delirium (mean (SD): 283.35 (27.97) µm vs 273.57 (20.14) µm, p=0.013). The schematic diagram of the macular thickness scan is shown in figure 2. Interestingly, such differences did not appear in the left macular, bilateral peripapillary RNFL or mGC-IPL thicknesses.

Given that gender may affect the retinal layer thickness and the susceptibility of postoperative delirium, we performed further analysis to compare retinal layer thickness and the incidence/severity of postoperative delirium between male and female participants. Results indicated that there were no significant gender differences in the average macular thickness, peripapillary RNFL thickness or mGC-IPL thickness, as well as the incidence or severity of postoperative delirium (p>0.05) (see online supplemental table 2).

Preoperative macular thickness associated with postoperative delirium

In the present study, the preoperative macular thickness of the right eye was significantly associated with the incidence of postoperative delirium before (OR 1.521, 95% CI 1.055 to 2.193, p=0.025) and after adjustment for age, sex and preoperative MMSE score (adjusted OR 1.593, 95% CI 1.093 to 2.322, p=0.015) in the participants. The macular thickness of the left eye, bilateral peripapillary RNFL thickness or mGC-IPL thickness was not associated with the incidence of postoperative delirium (see table 2).

Furthermore, the preoperative macular thickness of the right eye was statistically associated with the severity of postoperative delirium before (β=0.233, 95% CI −0.011 to 0.478, p=0.061) and after adjustment for age, sex and preoperative MMSE score (adjusted β=0.256, 95% CI 0.037 to 0.476, p=0.022) in the participants. Consistently, the preoperative macular thickness of the left eye, bilateral peripapillary RNFL

Table 1 Demographic and clinical characteristics of the study population

Variables (n=169)	Delirium (n=40)	Non-delirium (n=129)	t/χ^2/Z	P value*
Age (years), mean (SD)	71.53 (4.48)	71.04 (4.33)	0.62	0.539
Sex, female, n (%)	24 (60%)	72 (56%)	0.22	0.641
Education (years), mean (SD)	7.45 (4.14)	8.76 (4.16)	−1.74	0.084
BMI (kg/m^2), mean (SD)	26.37 (5.09)	25.00 (3.28)	1.61	0.115
Hypertension, n (%)	21 (53%)	64 (50%)	0.11	0.750
CCI (points), n (%)				
2	6 (15%)	26 (20%)		
3	11 (28%)	37 (29%)		
4	15 (38%)	37 (29%)	1.41	0.856
5	6 (15%)	23 (18%)		
≥6	2 (5%)	6 (5%)		
MMSE (points), median (IQR)	25.00 (24.00–27.00)	27.00 (25.50–28.00)	−3.59	**< 0.001**
ASA class, n (%)				
I	1 (3%)	6 (5%)		0.387
II	33 (83%)	113 (88%)	2.04	
III	6 (15%)	10 (8%)		
Length of anaesthesia (min), mean (SD)	167.74 (83.38)	142.97 (63.87)	1.91	0.058
Length of surgery (min), mean (SD)	123.18 (69.24)	104.02 (58.81)	1.66	0.099
Estimated blood loss (mL), mean (SD)	240.92 (54.16)	197.20 (23.31)	0.85	0.395
Postoperative WBC (10^9/L)	10.58 (3.93)	10.08 (2.93)	0.71	0.483
Postoperative NE (%)	82.04%	80.58%	0.88	0.382
Postoperative CRP (mg/L)	32.59 (5.80)	34.30 (3.74)	−0.23	0.817
IOP (mm Hg), mean (SD)	13.43 (2.60)	13.05 (2.49)	0.84	0.405
Right eye	13.14 (2.67)	12.92 (2.68)	0.46	0.650
Left eye	13.73 (2.81)	13.19 (2.63)	1.12	0.266
Macular thickness (μm), mean (SD)	280.14 (17.57)	273.57 (17.02)	2.12	**0.036**
Right eye	283.35 (27.97)	273.84 (20.14)	2.50	**0.013**
Left eye	276.93 (14.94)	273.84 (19.34)	0.93	0.357
Peripapillary RNFL thickness (μm), mean (SD)	94.88 (9.83)	94.61 (9.81)	0.15	0.884
Right eye	95.87 (9.87)	95.23 (11.28)	0.32	0.750
Left eye	93.88 (12.06)	93.99 (10.97)	−0.06	0.956
mGC-IPL thickness (μm), mean (SD)	76.95 (9.32)	78.32 (8.88)	−0.84	0.401
Right eye	78.26 (12.21)	78.35 (10.72)	−0.05	0.962
Left eye	75.65 (12.45)	78.30 (11.33)	−1.26	0.210

*Statistically significant results are shown in boldface.
ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CRP, C-reactive protein; IOP, intraocular pressure; IQR, interquartile range; mGC-IPL, macular ganglion cell-inner plexiform layer; MMSE, Mini-Mental State Examination; NE, neutrophil percentage; RNFL, retinal nerve fibre layer; SD, standard deviation; WBC, white blood cell count.

thickness or mGC-IPL thickness was not associated with the severity of postoperative delirium in the participants (see table 3).

DISCUSSION

Main findings

In the present study, we observed that the participants who developed postoperative delirium had greater macular thickness of the right eye than those who did not. Moreover, greater preoperative macular thickness of the right eye, rather than bilateral peripapillary RNFL thickness or mGC-IPL thickness, was associated with the incidence and severity of postoperative delirium. Our findings provided initial evidence indicating that preoperative macular thickness measured by OCT might serve as a useful non-invasive marker for the vulnerability of

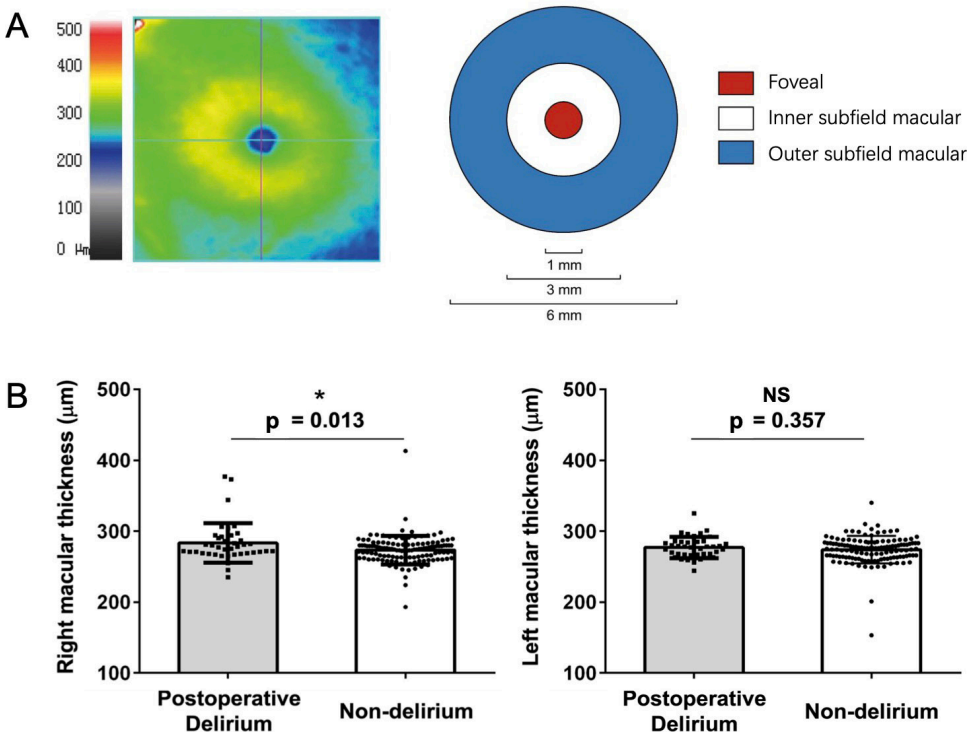

Figure 2 Comparison of macular thickness between participants with and without postoperative delirium. (A) Schematic diagram of macular thickness scan. (B) Participants with postoperative delirium had thicker macula than those without postoperative delirium in their right eyes, while no significant difference was observed in the macular thickness of their left eyes. NS, non-significant.

developing postoperative delirium in the older surgical population.

Retinal layer thickness has been frequently demonstrated to be related to cognitive impairment and has been suggested as a convenient and non-invasive AD biomarker. However, studies among patients with preclinical AD have reported conflicting results. Knoll *et al* found a significant relationship between thickening peripapillary RNFL thickness and poorer specific cognitive domains in patients with amnestic MCI and suggested that the paradoxically increased RNFL thickness might be due to inflammation or gliotic reactive changes.[16] In particular, Ascaso *et al* indicated that patients with amnestic MCI also had thicker macular thickness in comparison with the participants with normal cognition and patients with AD.[15] A recent study consistently revealed that the macular thickness instead of peripapillary RNFL thickness was associated with cognitive decline

Table 2 The association between retinal layer thickness and the incidence of postoperative delirium

Variables*	Unadjusted			Adjusted for age, sex and preoperative MMSE		
Incidence of postoperative delirium	**OR (95% CI)**	**Wald**	**P value†**	**OR (95% CI)**	**Wald**	**P value†**
Macular thickness						
Right eye	1.521 (1.055 to 2.193)	5.040	**0.025**	1.593 (1.093 to 2.322)	5.871	**0.015**
Left eye	1.201 (0.815 to 1.768)	0.859	0.354	1.238 (0.810 to 1.892)	0.970	0.327
Peripapillary RNFL thickness						
Right eye	1.060 (0.743 to 1.512)	0.103	0.748	1.074 (0.736 to 1.567)	0.136	0.712
Left eye	0.990 (0.694 to 1.412)	0.003	0.955	0.988 (0.674 to 1.449)	0.004	0.952
mGC-IPL thickness						
Right eye	0.992 (0.704 to 1.397)	0.002	0.962	0.960 (0.665 to 1.385)	0.048	0.826
Left eye	0.816 (0.592 to 1.125)	1.539	0.215	0.794 (0.566 to 1.113)	1.787	0.181

*Retinal layer thickness of bilateral eyes was scaled with Z scores in each model. Therefore, OR was reported per SD change in the retinal layer thickness.
†Statistically significant results are shown in boldface.
CI, confidence interval; mGC-IPL, macular ganglion cell-inner plexiform layer; MMSE, Mini-Mental State Examination; OR, odds ratio; RNFL, retinal nerve fibre layer; SD, standard deviation.

Table 3 The association between retinal layer thickness and the severity of postoperative delirium

Variables*	Unadjusted			Adjusted for age, sex and preoperative MMSE		
Severity of postoperative delirium	β Coefficient (95% CI)	t	P value†	β Coefficient (95% CI)	t	P value†
Macular thickness						
Right eye	0.233 (-0.011 to 0.478)	1.885	0.061	0.256 (0.037 to 0.476)	2.305	**0.022**
Left eye	0.176 (-0.070 to 0.421)	1.411	0.160	0.168 (–0.055 to 0.392)	1.485	0.144
Peripapillary RNFL thickness						
Right eye	0.018 (-0.229 to 0.266)	0.147	0.883	0.001 (–0.224 to 0.226)	0.007	0.994
Left eye	0.007 (-0.240 to 0.254)	0.055	0.956	–0.031 (–0.258 to 0.196)	–0.268	0.789
mGC-IPL thickness						
Right eye	0.017 (-0.222 to 0.257)	0.143	0.886	–0.042 (–0.262 to 0.178)	–0.374	0.709
Left eye	–0.060 (-0.295 to 0.175)	–0.501	0.617	–0.086 (–0.298 to 0.125)	–0.804	0.423

*Retinal layer thickness of bilateral eyes was scaled with Z scores in each model. Therefore, β coefficients represented the mean difference in delirium severity per SD change in the retinal layer thickness.
†Statistically significant results are shown in boldface.
CI, confidence interval; mGC-IPL, macular ganglion cell-inner plexiform layer; MMSE, Mini-Mental State Examination; RNFL, retinal nerve fibre layer; SD, standard deviation.

among community-dwelling participants, suggesting that macular degeneration might precede peripapillary RNFL in the early stage of cortical degeneration.[17] These findings demonstrated that retinal layer thickening, especially in the macular area, could be a sensitive feature of individuals at an early stage of AD, such as MCI. In the current study, we observed that participants with greater macular thickness measured before surgery were more likely to develop postoperative delirium. Since macular degeneration, such as increased fibrosis and thickness, has been observed in patients with AD in the early stages of the illness, these findings further suggest a potential pathogenesis overlap between delirium and AD.

The cause behind the thickening of retinal structures during the early stages of neurodegeneration remains uncertain. The macula contains mostly bodies of retinal neurons and is more vulnerable to extracellular deposits of Aβ, chronic inflammation and oxidative stress. Processes such as neuroinflammation,[18] the accumulation of denatured proteins both inside and outside cells, such as Aβ deposition,[19] are already underway within retinal layers. Moreover, these pathologic changes could potentially lead to the swelling of neurons, often referred to as ballooned neurons, which might disrupt the blood–retinal barrier and result in the demise of retinal neurons.[20] These mechanisms might contribute to the thickening of the macula. In addition, previous studies have consistently suggested that macula thickening was not only attributed to retinal neuron swelling but also to reactive gliosis, including the proliferation and activation of retina glial and Müller cells, which are closely associated with greater vulnerability.[21] In combination, the outcomes of the present study indicated that thicker macula was associated with postoperative delirium, further supporting a hypothesis that older adults who develop postoperative delirium could be at a preclinical stage of AD. Delirium is more likely to occur when such individuals are stressed by environmental factors such as anaesthesia and surgery. Notably, the macula, distinguished by its high concentration of neurons, photoreceptors, and neuron fibre layers, could potentially be more susceptible to retinal neurodegeneration, thus potentially serving as a marker for identifying individuals at high risk of developing postoperative delirium.

We found interocular differences in macular thickness among patients with postoperative delirium, with the right eye showing thicker macular thickness than the left eye. Furthermore, the association of macular thickness and postoperative delirium only appeared in the right eye but not the left. The mechanisms behind the interocular differences in macular thickness in patients with postoperative delirium are not currently well understood. However, asymmetry of neurodegeneration in both the retina and brain has been frequently observed. Several previous studies have investigated the interocular RNFL asymmetry in normal subjects using OCT and consistently indicated that the average retinal layer thickness in the right eye was thicker than in the left eye. The interocular difference remained stable with ageing.[22] Specifically, significant interocular asymmetry has been demonstrated histologically, and findings have contributed to the difference in density of retinal ganglia cells, glial and Müller cells, or both.[23] The degree of hemisphere asymmetry is considered to be associated with the severity of AD-related symptoms.[24] Similarly, interocular difference in average RNFL thickness has been considered a predictive factor for early glaucomatous optic neuropathy.[22] However, it remains unknown whether the unilateral association between macular thickening of the right eye and postoperative delirium could be attributed to the asymmetry of retinal degeneration. In addition, previous studies have demonstrated that hippocampus subfields have characteristics of hemispheric asymmetry, and the sub-regional volume of the left hippocampus

was smaller than that of the right hippocampus.[25] It has been supposed that the possible reason for a negative link between left hippocampus atrophy and cognition was that the volume of subfields was small, especially for the left hippocampus, potentially weakening the statistical power due to floor effects.[26] Similarly, OCT studies demonstrated that retinal layer thickness in the left eye was thinner than that in the right eye, so the floor effects might partially explain the observation that the association of macular thickness and postoperative delirium only appeared in the right eye but not the left. The results from the present study indicated that the macular thickness of the right eye might be indicative in the early identification of individuals at higher risk of developing postoperative delirium.

Although we have adjusted gender as a confounder when investigating the association between retinal layer thickness and the development of postoperative delirium, we wanted to assess whether there is a difference between men and women. Previous studies indicated substantial effects of gender on retinal layer thickness, with specific patterns for different sectors.[27] However, in the present study, there was no significant difference in the macular or RNFL thickness between men and women. In addition, it has been demonstrated that men and women had different susceptibilities to delirium and some other psychiatric disorders, such as schizophrenia, in various life stages.[28 29] Specifically, the prevalence of illness was higher among men in young adults while higher among women in the elderly population, which might contribute to the neuroprotective functions of oestrogen effects. However, we did not find any gender differences related to the development of postoperative delirium among participants older than 65 years. A prospective cohort study with a larger sample size is required to explore further the gender-specific effects on retinal layer thickness and postoperative delirium in the elderly surgical population.

Limitations

The study has several limitations. First, the potential confounding factors could influence the conclusion that the preoperative thickening macula of the right eye was associated with the development of postoperative delirium. We thus have strictly adjusted the confounding factors, including age, sex and preoperative MMSE scores in all multivariable models. However, we did not examine the eye dominance of the participants in the present study, which might cause bias in the interpretation of the results regarding the association between the preoperative thickening macula of the right eye and the development of postoperative delirium. Second, the sample size was small, relatively lacking in diversity and was recruited from only one hospital, which may restrict the generalisability of current conclusions. Future studies with larger sample sizes are warranted to confirm our findings.

Implications

The current findings indicated that preoperative macular thickness of the right eye was associated with the incidence and severity of postoperative delirium. Pending further validation in larger samples, our findings suggest that macular thickness measured by OCT may serve as a non-invasive marker and identify individuals vulnerable to developing postoperative delirium after anaesthesia and surgery among geriatric patients.

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Funding This study was supported by grants from National Natural Science Foundation of China (81720108012, 82001118), Ministry of Science and Technology of China (2021ZD0202003), Shanghai 'Rising Stars of Medical Talents' Youth Development Program (SHWSRS(2023)-62), and Henry K. Beecher Professorship from Harvard University.

Competing interests ZX provided consulting services to Shanghai 9th and 10th People's Hospitals, Baxter (invited speaker), NanoMosaic, and Journal of Anesthesiology and Perioperative Science in the last 36 months.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Institutional Review Board (IRB # SHSY-IEC-3.0/15-78/01) at Shanghai 10th People's Hospital. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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