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Ethics and Policies

Ethical Responsibilities and Policies

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ORIGINAL ARTICLES

LETTER TO THE EDITOR

CASE REPORTS

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Original Article

One-Year Visual, Refractive, Tomographic, and Aberrometric Outcomes of Repeat Corneal Collagen Crosslinking in Eyes with Progressive Keratoconus

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Abstract

Objectives: To evaluate visual, refractive, tomographic and aberrometic outcomes of repeat corneal collagen crosslinking (CXL) using Dresden protocol in the management of keratoconus progression at 1-year follow-up.

Methods: Charts of consecutive progressive keratoconus patients who underwent repeat corneal collagen CXL using Dresden protocol and had at least 1 year follow-up were retrospectively evaluated. Best spectacle-corrected distance visual acuity (CDVA), manifest refraction, slit lamp biomicroscopy, corneal tomography, corneal aberrometry and endothelial cell counts were evaluated before repeat CXL and at postoperative year-1. At postoperative 1-month, corneal demarcation line depth were evaluated using anterior segment optic coherence tomography.

Results: Overall, seven eyes of seven patients with the mean age of 23 (ranged 19 to 27) years were included. The interval between the initial and repeat CXL procedures was 60 (ranged 28 to 89) months. At postoperative month-1, a clear demarcation line could be observed in all patient eyes. The mean demarcation line depth was 250 (ranged 220 to 360) µm. At postoperative month-12, mean CDVA, manifest refraction, topographic indices, and aberrometric outcomes remained stable ($p>0.05$). Maximum keratometry was reduced more than 1D in two (28.6%) eyes, and remained stable in the remaining five (71.4%) eyes. No significant endothelial cell loss or any other sight-threatening complication was encountered in any patient eye.

Conclusion: Repeat corneal CXL seems to be safe and effective in halting keratoconus progression at 1-year follow-up.

Keywords: Corneal collagen crosslinking, keratoconus, repeat crosslinking, retreatment, progression

Introduction

Keratoconus is a chronic, bilateral corneal ectatic condition characterized by progressive stromal thinning and anterior protrusion of the corneal surface. These structural alterations lead to irregular astigmatism and myopia, and in more advanced stages, visual deterioration secondary to corneal scarring may ocur (1). Corneal collagen crosslinking (CXL) is the only procedure that has been shown to effectively halt the progression of corneal ectasia in keratoconus (2).

Following the initial report by Wollensak et al. (2) in 2003, the safety and efficacy of this procedure in both adult and pediatric patients with keratoconus have been demonstrated by several prospective cohort studies as well as randomized controlled trials(3-5). Corneal CXL has become one of the standard treatments of progressive keratoconus

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and various protocols of CXL have been evolved over the last decade (6,7).

While CXL has demonstrated high success rates in halting keratoconus progression, some cases still exhibit post-treatment progression, accompanied by worsening keratometric, refractive, and pachymetric parameters. In long term follow-up studies, progression rate after initial conventional CXL was up to 11% (8-12), whereas that for other modified procedures was as high as 24% (13). However, whether repeat CXL may further help in stabilizing the cornea in progressive cases, or the ideal protocol to use in repeat surgeries, or the ideal interval between repeat and initial CXL surgeries remain unknown.

This study aims to evaluate the visual, refractive, topographic and aberrometric outcomes of repeat CXL in the management of keratoconus progression at 1-year follow-up.

Materials and Methods

The study was approved by the IRB Committee (No: İ01-101-25, Date: 17.02.2025). Prior to enrollment, written informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

The files of consecutive progressive keratoconus cases who underwent repeat corneal CXL between July 2010 and January 2022, and who had at least 1 year follow-up were reviewed retrospectively. In all eyes, progression was established based on sequential analyses of corneal topography, pachymetry, visual acuity, manifest refraction. Progression after initial CXL was defined as an increase of more than 1.0 Diopters (D) in the maximum keratometry (Kmax) values, accompanied by a decline in best spectacle-corrected distance visual acuity (CDVA) after postoperative month-6 (14).

Eyes presenting with advanced axial stromal scarring, a previous episode of herpetic keratitis, concurrent corneal or ocular pathology other than keratoconus, or any autoimmune disorder were excluded from the study. Patients who had been wearing rigid gas-permeable contact lenses discontinued lens use at least four weeks prior to CXL, whereas those using soft contact lenses ceased wear for a minimum of two weeks.

Surgical Technique

Following instillation of topical anesthesia with 0.5% proparacaine hydrochloride, the central 8.0–9.0 mm corneal epithelium was mechanically debrided. Riboflavin solution (MedioCross D, Peschke Meditrade GmbH, Germany) was instilled onto the corneal surface every two minutes for a total of 30 minutes. Adequate stromal and anterior chamber riboflavin penetration was verified using slit-lamp biomicroscopy. Intraoperative pachymetric assessment confirmed that corneal thickness exceeded 400 μm prior to irradiation. Ultraviolet-A (UVA) illumination was then applied with an irradiance of 3.0 mW/cm² for 30 minutes using the UV-X system (IROC AG, Switzerland), while riboflavin drops were reapplied every two minutes during exposure. Upon completion, a therapeutic soft contact lens was fitted, and topical antibiotic drops were prescribed four times daily for one week. Patients were advised to avoid eye rubbing and to wear protective sunglasses. After epithelial healing, the bandage lens was removed, and topical corticosteroid therapy was initiated at four times daily, gradually tapered over two weeks and discontinued after one month.

Pre- and Post-operative Evaluation

Preoperatively and at postoperative month-1, -3, -6, and -12 all patients had detailed ophthalmologic examination that included uncorrected distance visual acuity (UDVA), best spectacle-corrected distance visual acuity (CDVA), manifest refraction (MR), slit lamp biomicroscopy, corneal tomography, pachymetry and aberrometry (Pentacam, Oculus GmbH, Wetzlar, Germany), ultrasonic (US) pachymetry (Accupach VI pachymetry, Accutome, PA, USA), in vivo confocal microscopy (IVCM; HRT II, Rostock Cornea Module,Heidelberg, Germany), and anterior segment optical coherence tomography (AS-OCT; Visante, Carl Zeiss Meditec, Dublin, CA, USA).

At least three topography scans were obtained from each patient eye at every follow-up visit. The highest-quality maps were selected for analyses. The corneal thickness, sagittal curvature, anterior elevation, and posterior elevation measurements were evaluated at baseline and during all postoperative visits.

Endothelial cell count (ECC) and structural alterations in the corneal stroma were assessed using IVCM. Presence and depth of demarcation line were determined with AS-OCT at postoperative month-1. During the AS-OCT examination, patients were asked to fixate on the central target within the device and images were acquired in the horizontal meridian centered on the corneal apex, and the measurement of DLD was performed at the very center of the OCT image. Measurement and interpretation of DLD with AS-OCT were performed by the same investigator (TCB).

Outcome Measures

The primary outcome measure was the efficacy of repeated CXL procedure in the first postoperative year. Effective CXL was defined as stable and/or decreasing Kmax values of the steepest axis on corneal tomography at postoperative year-1. The secondary outcome measures were visual, refractive and keratometric outcomes, the demarcation line depth after repeat CXL and safety of the procedure. Safety was defined as no significant reduction in endothelial cell

count beyond the physiological loss. Safety was defined as no endothelial cell count beyond the physiological loss. Safety was considered to be maintained when endothelial cell density remained within the expected range of physiological variation.

Statistical Analysis

Continuous variables were summarized as median with range (mean±standard deviation), while categorical variables were expressed as frequency and percentage. The normality of distributions was assessed using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. To evaluate the effect of time on the variables, either paired-samples t-tests or Wilcoxon signed-rank tests were applied, depending on data distribution. All statistical analyses were conducted using SPSS software (Version 26.0; IBM Corp., Chicago, IL), and a p-value of less than 0.05 was considered statistically significant.

Results

During the 2010 to 2022 study period, 880 eyes of 528 patients were treated with CXL procedures in our clinic. Among these, nine eyes of nine patients diagnosed to have progression after initial CXL (1.03%), and underwent repeat CXL. Seven eyes of seven patients had at least 12 months follow up.

Initial CXL was performed using conventional Dresden protocol in six eyes and accelerated CXL protocol (9 mW/cm2 UVA for 10 minutes with 30 minutes dextran-based riboflavin imbibition) in one eye (Table 1). The median interval between the initial and repeat CXL procedures was 60.0 (range, 28 to 89; mean, 60.4±20.6) months. Patients characteristics before repeat CXL were shown in Table 1. At the time of repeat treatment, the median age was 23 (range, 19 to 27; mean, 18.1±3.3) years. Eye rubbing was present in three (42.9%) eyes.

At baseline, median UDVA and CDVA were 0.31 (range, 0.00 to 1.0; mean, 0.40±0.31), and 0.10 (range, 0 to 0.40; mean, 0.16±0.15) logMAR, respectively. Manifest refraction spherical equivalent (MRSE) was -5.25 (range, -8.50 to -0.25; mean, -4,43±3,22) D. At postoperative month-12, median UDVA (p=1.000), CDVA (p=0.317), and MRSE (p=0.655) remained stable. Overall, in 28.6% of cases CDVA improved at least two Snellen lines, with no cases losing one or more lines.

At baseline, prior to repeat CXL, Kmax was <55D in two eyes (28.6%), 55-58D in one eyes (14.3%) and >58D in four eyes (57.1%) (Table 1). The median flattenning in Kmax was -0.66 (range, 0 to -1.8) D. At postoperative month-12, more than 1D flattenning of Kmax was observed in two eyes (28.6%), whereas Kmax remained stable in the remaining five eyes (71.4%). At the first postoperative year, none of the eyes showed a progression greater than 1 D in Kmax (Table 1).

The median Kf, Ks, Kmax, MAE, ISV, IVA, KI, CKI, Max PI, and vertical coma remained stable at postoperative year-1 (Table 2).

One month after initial CXL, demarcation line depth measurement was available in only two patients eyes (at 220 µm depth [43%] and at 230 µm depth [45%]). Prior to the repeat CXL, AS-OCT was performed in 5/7 patients eyes 56 (range, 1 to 61) months after initial CXL. Hyperreflective area suggesting stromal demarcation line was visible at the median depth of 220 (range, 200 to 280) µm (Fig. 1). At postoperative month-1, a clear demarcation line at AS-OCT could be observed in all patient eyes. The median demarcation line depth was 250 (range, 220 to 360) µm. The median percentage of the demarcation line depth compared to the total corneal thickness was 47.0% (range, 35.7 to 50.9) prior to the repeat CXL, and 60.0% (range, 41.5 to 69.0) at postoperative month-1.

At baseline, the median ECD was 2538.5 (range, 1540 to 3050) cells/mm^2 and remained stable at postoperative year-1 (median, 2358; range, 1927 to 2957; p=0.063).

Complete epithelial closure was observed in all eyes by postoperative day-4. The median time to epithelization was three (range, 3 to 4) days. Two eyes (28.6%) had moderate corneal stromal haze at postoperative week-1. However, with frequent use of topical (n=2) and systemic (n=2) corticosteroids, corneal stromal haze resolved in all eyes. At postoperative month-1, all corneas were clear. Corneal complications including scaring, infections, recurrent epithelium erosion, corneal melting or perforation were not noted in any patients eyes during follow-up.

All fellow eyes of cases had previously undergone CXL and were followed for a median duration of 84.0 (range, 70-124; mean, 93.0±21.2) months. None of these eyes demonstrated signs of progression during the follow-up period.

Discussion

In our study, repeat corneal CXL provided visual, refractive, keratometric, and aberrometric stabilization in progressive keratoconus cases. Additionally, visible demarcation line with the depth of 250 µm indicated further crosslinking in corneal stroma. No significant endothelial cell loss or any other clinically significant adverse event was encountered in any patient eye during follow-up.

It is well known that not all corneas respond in the same way to corneal CXL. There are variety of parameters that might affect visual, refractive and topographic outcomes of the treatment. Preoperative Kmax value, corneal thickness, patients age, presence or absence of eye rubbing, as well as the choice of CXL protocol were suggested to affect progression of keratoconus after initial CXL (15,16). In our study, due to the limited number of retreated cases, it was

Table 1. Patients characteristics and change in progression indices over time following initial and repeat corneal collagen crosslinking

Case	Age* (year), Sex	Initial CXL		Initial CXL						Repeat CXL		Time interval (month)
				Preop	Year-1	Year-2	Year-3	Year-4	Year-5	Preop	Year-1	
1	16, F	C-CXL	Kmax (D)	55.5	57.4	56.7	56.7	58.3	57.6	58.0	57.6	57
			TCT (µm)	425	402	419	427	421	406	405	407	
			MRSE (D)	-10.0	-8.50	-8.50	-8.50	-8.50	-8.50	-8.50	-7.25	
			CDVA (logMAR)	0.3	0.22	0.22	0.22	0.22	0.22	0.22	0.22	
2	19, M	C-CXL	Kmax (D)	47.1	47.5	47.3			47.5	48.4	46.6	89
			TCT (µm)	519	513	521			515	518	497	
			MRSE (D)	-1.5	0.0	0.0			0.0	-0.25	-0.25	
			CDVA (logMAR)	0.0	0.0	0.0			0.0	0.0	0.0	
3	22, M	C-CXL	Kmax (D)	58.9	59.9	61				60.2	60.0	28
			TCT (µm)	500	491	487				494	467	
			MRSE (D)	-5.75	-4.75	-4.75				-5.25	-5.75	
			CDVA (logMAR)	0.22	0.10	0.10				0.10	0.10	
4	14, F	C-CXL	Kmax (D)	48.8	48.3	49.1	49.9	50.5	50.7	50.7	50.0	61
			TCT (µm)	515	507	525	515	505	529	529	502	
			MRSE (D)	-1.0	-0.25	-0.25	-1.0	-0.75	-1.0	-1.0	-1.0	
			CDVA (logMAR)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
5	23, F	A-CXL	Kmax (D)	56.4	56.6	57.6	56.9	58.2		58.2	58.2	46
			TCT (µm)	444	446	446	445	436		436	424	
			MRSE (D)	-6.0	-6.0	-6.0	-6.0	-6.0		-6.0	-6.0	
			CDVA (logMAR)	0.4	0.4	0.3	0.3	0.3		0.3	0.3	
6	16, M	C-CXL	Kmax (D)	61.8	61.2	60.5	60.0	61.8	61.8	62.9	62.9	83
			TCT (µm)	470	466	442	472	465	461	467	449	
			MRSE (D)	-4.25	-2.50	-2.5	-2.5	-2.5	-2.5	-2.50	-2.5	
			CDVA (logMAR)	0.22	0.15	0.10	0.10	0.10	0.10	0.10	0.10	
7	17, F	C-CXL	Kmax (D)	61.9	61.6		62.1		63.3	63.3	61.8	60
			TCT (µm)	402	417		414		410	407	408	
			MRSE (D)	-10.50	-3.25		-3.25		-7.50	-7.50	-6.50	
			CDVA (logMAR)	0.52	0.22		0.22		0.40	0.40	0.22	

A-CXL: accelerated crosslinking; CDVA: best spectacle-corrected distance visual acuity; CXL: crosslinking; C-CXL: conventional crosslinking; F: female; Kmax: maksimum keratometry; M: male; MRSE: manifest refraction spherical equivalent; Preop.: preoperative; TCT: thinnest corneal thickness; [a]: Time interval between the initial CXL and repeat CXL. *: Age at the time of initial corneal collagen crosslinking

Table 2. The pachymetric, keratometric, topographic and aberrometric outcomes before and after the repeat corneal collagen crosslinking

	Before repeat CXL	At postoperative year-1 after repeat CXL	p
CCT	492.00 (429.0-537.0) (483.56±44.22)	462.00 (433.0-506.0) (465.75±35.07)	0.144
TCT	467.00 (405.0-529.0) (465.14±50.92)	443.00 (408.0-497.0) (447.75±41.64)	0.144
Kf	48.1 (42.30-49.80) (46.8±3.1)	46.0 (40.90-48.80) (45.4±3.6)	0.114
Ks	51.50 (45.90-55.00) (51.1±3.2)	51.15 (43.70-53.90) (50.0±4.5)	0.068
Km	49.30 (44.00-52.10) (48.9±2.9)	48.40 (42.30-51.20) (48.0±4.5)	0.068
Kast	3.80 (1.80-8.90) (4.3±2.4)	3.95 (2.10-8.10) (4.5±2.7)	0.066
Kmax	58.20 (48.40-63.30) (57.39±5.77)	59.10 (46.20-61.80) (56.65±6.86)	0.109
ISV	99.00 (40.00-120.00) (87.43±34.85)	118.00 (39.00-124.00) (93.67±47.44)	1.000
IVA	0.96 (0.31-1.39) (0.87±0.42)	1.19 (0.41-1.51) (1.04±0.57)	0.414
KI	1.16 (1.05-1.38) (1.21±0.12)	1.32 (1.08-1.39) (1.26±0.16)	0.414
CKI	1.10 (1.02-1.14) (1.08±0.05)	1.08 (0.99-1.13) (1.07±0.07)	0.414
Rmin	5.80 (5.33-6.97) (5.93±0.64)	5.80 (5.46-7.24) (6.17±0.94)	0.180
IHA	43.60 (8.80-55.20) (36.23±15.37)	28.10 (10.10-35.20) (24.47±12.94)	0.593
IHD	0.16 (0.03-0.19) (0.12±0.07)	0.18 (0.04-0.20) (0.14±0.09)	1.000
MAE	34.00 (12.00-41.00) (29.71±10.86)	34.00 (16.00-39.00) (30.75±10.63)	0.465
Max PI	3.40 (1.80-3.50) (2.97±0.69)	3.75 (2.20-4.70) (3.60±1.06)	0.180
Vertical coma	-2.038 (-4.18--0.38) (-2.098±1.383)	-2.010 (-3.64--0.77) (-2.109±1.317)	0.144
Spherical aberration	-1.288 (-1.95-0.01) (-0.978±0.762)	-0.979 (-1.43-0.48) (-0.726±0.893)	0.273

Values are presented as Median (Min-Max) and (Mean ± Standard Deviation). P: Influence of time on variables, paired samples t test or Wilcoxon signed rank test. CCT: central corneal thickness; CKI: central keratoconus index; Kast: keratometric astigmatism; Kf: flat keratometry; Ks: steep keratometry; Km: mean kertometry; KI: keratoconus index; IHA: index of height asymmetry; IHD: index of height decentration; ISV: index of surface variance; IVA: index of vertical asymmetry; MAE: maximum anterior elevation at central 5 mm; Max PI: Maximum progression index; Rmin: minimum sagittal curvature at central 8.0 mm; TCT: thinnest corneal thickness

difficult for us to assess the individual influence of such parameters on progression. However, all patients who needed repeat CXL were less than 23 years of age at the time of initial CXL. Therefore one might hypothesize, young age might be a risk factor for CXL failure. However, all fellow eyes of patients had previously undergone CXL and were followed for a median duration of 84 months. None of these eyes demonstrated signs of progression during the follow-up period. In regards to the potential effect of the initial CXL protocol on keratoconus progression, statistical analysis was not feasible because of the unequal distribution between treatment groups (six eyes treated with the conventional Dresden protocol and one eye with accelerated CXL protocol).

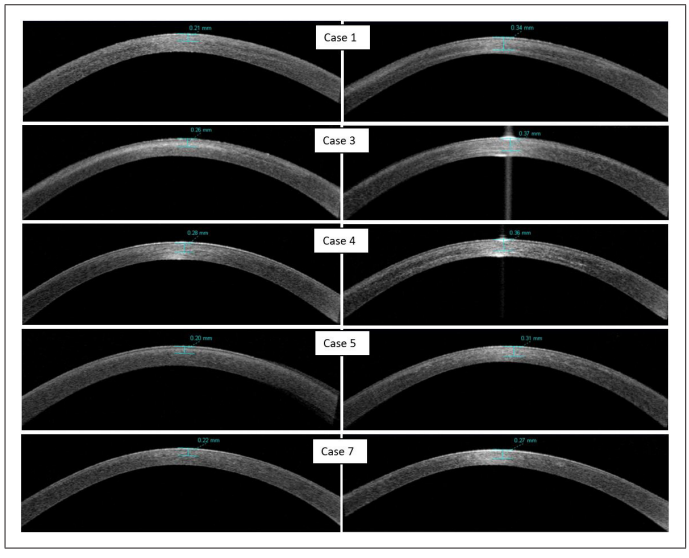

Figure 1. Demarcation lines measured by anterior segment optical coherence tomography before (left column) and 1 month after (right column) repeat CXL in 5 patients eye.

Repeat CXL was first described by Hafezi et al. (17) in a progressive keratoconus patient 4 years after the initial CXL procedure. The authors reported further flattening effect following the repeat CXL procedure at postoperative year-2 (17). Later, several case reports described stabilization of ectasia up to 6 years following repeat CXL (18-20). Antoun et al. (21) investigated the safety and efficacy of repeat CXL treatment in 7 eyes, and reported stable visual outcomes and topographic measurements in all patients at postoperative year-1 (22,23). As for modified CXL protocols, 2 cohort studies reported stabilization of ectasia at 1 to 2 years follow-up following repeat-CXL using an accelerated protocol

(9 mW/cm^2, 10 minutes) (24,25). The largest series that has been published, evaluated the safety and efficacy of repeat transepithelial CXL in 21 eyes at 24 months follow-up (24). The authors reported that the procedure was effective in halting progression and induced formation of further cross-links in the corneal stroma using IVCM (24). Despite these studies, the best timing following the initial CXL procedure and the best CXL protocol for repeat CXL remain unclear. In our study, repeat CXL was performed 28 to 72 months (median, 60.5 months) after the initial CXL and Dresden protocol was used. Stabilization of ectasia was noted following repeat CXL treatment at postoperative year-1.

The above-mentioned clinical findings has not been confirmed by biomechanical or histopathological studies. Experimental studies conducted by Beshtawi et al. (25) in human corneas and by Tabiban et al. (26) in rat corneas reported that repeat CXL after 1-3 days did not provide any additional biomechanical stiffness. Recently, Zhang et al. (27) evaluated histopathological and biomechanical changes in the cat corneas after repeat CXL with a 1-month interval between treatments, and reported no additional benefit of repeated treatment. The conflicting results between clinical and experimental studies might be due to the differences in in-vivo and ex-vivo conditions. Moreover, in experimental studies, the time intervals between the initial CXL and repeat CXL were too short to detect any long-term remodelling changes of the corneal stroma. Therefore the results might be not fully applicable to clinical practice, in which the repeat CXL may be performed years after the initial CXL procedure and thus the initial effect of initial CXL may wear off.

In addition to those short-term histopathological outcomes, long-term remodelling effects of the corneal stroma could be evaluated by the demarcation line. Visibility and depth of demarcation line following repeat CXL has been rarely evaluated so far. Only in a case report by Hafezi et al. (17) it was mentioned that the visibility of stromal demarcation line was similar to that noted following initial CXL, and was at a depth of 250 to 300 µm. In our study, the demarcation line depth and percent ratio following repeat CXL were 250 µm and 60%, respectively. Since the demarcation line depth following the initial CXL procedure had been measured in only 2 patients eyes, no comparison between the two protocols could be done. Further studies are needed to understand whether repeat CXL induced deep stromal crosslinking following CXL in the previously remodelled corneas.

Another concern about repeat CXL is its safety. There is a possibility that the retreated cornea might be thinner within the first year of initial CXL, thus increasing the risk of endothelial toxicity. Besides, successive epithelial removals in epi-off procedures might increase the risk of postoperative complications such as prolonged corneal haze, sterile corneal infiltrates, recurrent corneal erosions and/or microbial keratitis. Histopathological analysis of cat corneas month-1 following repeat CXL revealed slightly swollen collagen fibers with slightly blurred borders, suggesting damage to the collagen fiber structure (27). Corneal haze was also more pronounced in the repeat CXL group compared to the one-time CXL group (27). However, in human corneas, Hafezi et al. (17) reported similar postoperative haze compared to those observed after a single CXL procedure. Recently, Grentzolas et al. (18) performed repeat CXL for a progressive keratoconus patient and reported non-clinically significant corneal haze at postoperative year-1. At postoperative year-6, cornea was clear and there were no endothelial cell loss or other complication. The corneal repair process in human corneas has been reported to take up to 6 months to 1 year. Previous cohort studies including 7 to 12 cases reported no major complications after repeat CXL (21-24). Similarly, in our study, no sight-threatening complication, prolonged haze or endothelial cell loss was encountered in any patient eye. However, prolonged epithelial healing in the early postoperative period was encountered somewhat more frequently than expected in retreated cases. Although the epithelial healing was achieved within 4 days in 2 patients eyes, it was longer than our clinical experience with initial CXL, which was 3 days (5,28).

There are several limitations in our study including retrospective design, short term follow-up and limited number of patient. Besides, some patients were lost to follow-up. However, considering the rare progression of keratoconus after initial CXL and limited number of reported studies on repeat CXL so far, we believe the results of our study may be important to the understanding of short term outcomes of repeat CXL in keratoconic eyes.

Conclusion

In conclusion, in this case series, repeat corneal CXL using Dresden protocol seems to be safe and effective in halting keratoconus progression at 1-year follow-up. Further studies with more number of patients and longer follow-up are required to establish evidence-based criteria as to the best CXL protocol to perform and the optimum time to re-treat.

Disclosures

Ethics Committee Approval: This study was approved by the Anakara University Ethics Committee (Date: 17/02/2025, No: İ01-101-25).

Informed Consent: Written informed consent was obtained from all participants,

Conflict of Interest The authors state no conflict of interest to disclose.

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Original Article

Prevalence of Occult Macular Pathologies Detected by Optical Coherence Tomography in Patients Scheduled for Cataract Surgery

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Abstract

Objectives: To investigate the prevalence of macular pathologies detectable only by optical coherence tomography (OCT) and not suspected on fundoscopic examination before cataract surgery in a large series of Turkish patients and to determine associated risk factors.

Methods: Medical records of patients who underwent cataract surgery, had normal fundoscopic findings during preoperative evaluation, and underwent macular OCT were retrospectively reviewed for demographic data, ophthalmological findings, and systemic examination results. Patients were divided into normal and abnormal OCT groups according to their macular OCT results. Patients in the abnormal OCT group were further analyzed for the prevalence of OCT-detected occult macular pathologies and associated risk factors.

Results: Data from 1.091 eyes were included in the study. Macular pathology was detected on OCT in 9.2% of patients. Among these patients, 40 (40%) had age-related macular degeneration, 31 (31%) had epiretinal membrane, 11 (11%) had vitreomacular traction, 8 (8%) had lamellar macular hole, 5 (5%) had diabetic macular edema, and 5 (5%) had macular pseudohole. The mean age of patients with occult macular pathology was significantly higher than that of patients with normal OCT findings (p=0.001). 78.0% of patients with retinal pathology were 70 years of age or older. Advanced age was identified as the most important predictor of occult macular pathology (OR: 1.086, p=0.001).

Conclusion: Reliance solely on fundoscopic examination would result in approximately 1 in 10 eyes with occult macular pathology being overlooked. OCT screening should be considered prior to cataract surgery, particularly in elderly patients.

Keywords: Cataract, preoperative assessment, optical coherence tomography, occult macular pathology

Introduction

With the continuous advances in phacoemulsification techniques and intraocular lens (IOL) technology, expectations for optimal postoperative visual outcomes have markedly increased among both surgeons and patients (1,2). Nonetheless, a discrepancy is sometimes observed between the anticipated and the actual visual results (3). Refractive errors and pre-existing ocular comorbidities are regarded as the leading factors contributing to such inconsistencies (4). Recent advances in biometric technologies and calculation formulas, along with improvements in IOL designs, have significantly improved refractive outcomes in cataract surgery (5). However, accompanying ocular comorbidities remain a significant problem, especially in countries with low socioeconomic status (4).

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Retinal pathologies and maculopathies are the leading ocular comorbidities that limit postoperative visual improvement (6,7). Identifying these pathologies is important for preoperative patient counseling, assessing their expectations, and planning postoperative follow-up. Dilated fundoscopic examination is the classic method of preoperative retinal assessment; however, media opacities may limit the quality of the information obtained. Optical coherence tomography (OCT) provides rapid, repeatable, and quantitative evaluation of the macula (8). Different opinions have been reported in the literature regarding the importance of preoperative OCT screening in eyes with normal fundoscopic appearance (9-11). Although there is general agreement that preoperative OCT is cost-effective in patients scheduled for multifocal IOL implantation, its routine use before standard cataract surgery remains a matter of debate (12).

In a survey of cataract surgery practices among 240 ophthalmologists from 38 countries showed that only 50% of participants performed preoperative OCT scanning (13). In previous studies, the prevalence of occult macular pathologies detectable by OCT prior to cataract surgery was reported to range from 4% to 42% (14-20). A recent review found that 13.7% of eyes deemed normal on fundoscopic examination harbored occult macular pathology preoperatively (21). Occult macular pathologies detected by OCT do not invariably restrict postoperative visual gain (16). These screening studies help identify patients at higher risk for occult macular pathology.

The aim of the present study was to contribute to the existing literature by evaluating the prevalence of occult macular pathologies detected through preoperative macular OCT screening in a large Turkish cohort scheduled for cataract surgery, in whom such pathologies were not suspected on biomicroscopic fundus examination. In doing so, we aimed to highlight the added value of preoperative OCT in identifying macular conditions that may be missed during routine fundus assessment. Additionally, we sought to determine factors predictive of abnormal OCT findings to guide screening priorities in settings where routine preoperative OCT may not be feasible.

Methods

Data from 1.091 eyes that underwent cataract surgery at the Department of Ophthalmology, Gulhane Faculty of Medicine, between May 2024 and May 2025 were reviewed in this retrospective study. The exclusion criteria were as follows: History of intraocular surgery, corneal disease (opacity, dystrophy, ectatic disease), mature cataract, uveal inflammation, glaucoma, presence of evident retinal pathology on fundoscopy, precluding adequate examination, age under 18 years, and poor cooperation. OCT scans with low signal strength (<7/10) were also excluded. The ethical principles of the Declaration of Helsinki were adhered to throughout the study. The study was approved by the Scientific Research Ethics Committee of the University of Health Sciences (approval number 2025-413).

Before the surgery, patients underwent a comprehensive ophthalmologic examination, including corrected distance visual acuity, slit-lamp microscopy of the anterior segment, dilated fundus examination, and intraocular pressure measurement. In patients with dense cataracts precluding retinal visualization, B-scan ocular ultrasonography was performed. Ocular biometric measurements were taken with the IOL Master 500 device (Carl Zeiss Meditec AG, Germany) and intraocular lens (IOL) power was calculated.

In our clinic, macular OCT evaluation is routinely performed before cataract surgery. Macular OCT imaging was conducted by an experienced technician using a spectral-domain OCT device (Heidelberg Engineering, Heidelberg, Germany). Based on the OCT findings, patients were categorized into two groups. The normal OCT group included patients with no pathology detected on OCT examination, while the abnormal OCT group included patients with vitreomacular interface diseases, macular edema, and age-related macular degeneration (AMD). OCT scans were reviewed independently by two investigators. All participants' OCT scans were evaluated for pathology and central macular thickness (CMT) measurements were also performed. OCT images with inconsistent findings and low signal strength (<7/10) were excluded from analysis. The severity of cataract was graded according to the Oxford Clinical Cataract Classification and Grading System (22). In addition to the patients' demographic and ophthalmological data, concomitant systemic diseases (diabetes, hypertension, cardiovascular disease, cerebrovascular disease) were also recorded.

Statistical Analysis

The sample size was determined by setting the statistical power ($1-\beta$) at a minimum of 80% and the Type I error (α) at 5% for each variable. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test and evaluation of skewness and kurtosis values. Since the data were normally distributed, parametric tests were applied. Descriptive statistics were presented as mean ± standard deviation, frequency (n), and percentage (%). Between-group comparisons of continuous variables were performed using the independent samples t-test. Multivariable binary logistic regression analysis was conducted to evaluate the association between patient factors and the odds of having abnormal OCT findings, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Associations between categorical variables were examined using the chi-square (χ^2) test. A p-value of <0.05 was considered statistically signifi-

cant. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Results

After 287 eyes were excluded from the study due to exclusion criteria, data from 1091 eyes were analyzed. The mean age of the patients was 69.56±9.3 years (range, 25–93), comprising 547 females (50.1%) and 544 males (49.9%). While pathology was observed in OCT in 100 patients (9.2%) of the eyes with normal fundoscopic examination, no pathology was detected in 991 patients (90.8%).

The mean age of patients with occult macular pathology on OCT (74.25±7.38 years) was significantly higher than that of patients with normal OCT findings (69.09±9.35 years; p=0.001). No significant differences were observed between the normal and abnormal OCT groups in terms of sex or the presence of systemic diseases (diabetes mellitus, hypertension, cardiovascular disease, and cerebrovascular disease) (all p>0.05) (Table 1). Based on fundoscopic examination findings, the following patients were excluded from the study: 1 Patient with adult-onset vitelliform dystrophy, 1 with asteroid hyalosis, 11 with degenerative myopia, 1 with Behçet's uveitis, 59 with diabetic retinopathy, 10 with epiretinal membrane (ERM), 88 with fundus examination obstructed due to dense cataract, poor cooperation, or OCT signal strength <7/10, 2 with chorioretinal coloboma or chorioretinal scar, 10 with full-thickness macular hole, 5 with optic neuropathy, 5 with a history of intraocular surgery, 4 with retinal vascular occlusion, 43 with drusen, and 47 with glaucoma.

The mean best-corrected visual acuity (BCVA) was 0.64±0.24 logarithm of the minimum angle of resolution (logMAR) (range, 0.30–1.00) in the normal OCT group and 0.67±0.24 logMAR (range, 0.40–1.00) in the abnormal OCT group. There was no significant difference in BCVA between the groups (p>0.05). The mean CMT was 252±17 µm in the normal OCT group and 259±24 µm in the abnormal OCT group, with no significant difference observed (p>0.05). No significant differences were found between the groups in terms of cataract type or nuclear cataract grade (all p>0.05). Table 2 shows the distribution of ophthalmological examination findings between the two groups.

Among the 100 patients with retinal pathology detected on OCT, 40 (40.0%) had drusen or changes in retinal pigment epithelium consistent with AMD, 31 (31.0%) had ERM, 11 (11.0%) had VMT, 8 (8.0%) had lamellar macular hole, 5 (5.0%) had macular pseudohole, and 5 (5.0%) had diabetic macular edema (DME). The distribution of occult macular pathologies seen in the study is shown in Table 3. The fundus photographs and OCT samples from these patients are shown in Figure 1. These patients were referred to retina specialists prior to surgery. Intravitreal anti-vascular endothelial growth factor injection was planned for a patient with AMD due to subretinal fluid and for a patient with DME due to clinically significant macular edema, and their surgeries were postponed. There were no changes to the treatment plans for other patients. The age distribution of the 100 patients with retinal pathology detected on OCT was as follows: 4 Patients were <60 years, 18 patients were 60–69 years, 56 patients were 70–79 years, and 22 patients were ≥80 years (Fig. 2). The proportion of patients aged 70 and over was 78.0%, while this proportion was 53.6% in the group without retinal pathology on OCT. Multivariable logistic regression analysis revealed that age was the only statistically significant predictor of abnormal OCT findings

Table 1. Demographic characteristics and systemic comorbidities of the patients

Parameters	Abnormal OCT (n=100)	Normal OCT (n=991)	p
Age (years)	74.25±7.38	69.09±9.35	**0.001***
Sex (male/female)	49 / 51	495 / 496	0.856⁺
Diabetes Mellitus	28 (28.0%)	288 (29.1%)	0.823⁺
Hypertension	32 (32.0%)	359 (36.2%)	0.401⁺
Cardiovascular Disease	20 (20.0%)	170 (17.2%)	0.475⁺
Cerebrovascular Disease	2 (2.0%)	14 (1.4%)	0.454⁺

OCT, optical coherence tomography. Significant p-values are shown in bold. Values are presented as number, percentage or mean ± standard deviation. *Independent-samples t-test, ⁺Chi-square test.

Table 2. Distribution of ophthalmological examination findings

Parameters	Abnormal OCT (n=100)	Normal OCT (n=991)	p
BCVA (logMAR)	0.67±0.24 (0.40-1.00)	0.64±0.24 (0.30-1.00)	0.336*
CMT (µm)	259±24	252±17	0.245*
NC Grade 2	35 (35.0%)	235 (23.7%)	0.412⁺
NC Grade 3	27 (27.0%)	199 (20.1%)	0.346⁺
NC Grade 4	5 (5.0%)	19 (1.91%)	0.214⁺
CC	1 (1.0%)	8 (0.8%)	0.262⁺
PSC	4 (4.0%)	97 (9.8%)	0.242⁺
Mixed	28 (28.0%)	433 (43.7%)	0.415⁺

OCT, optical coherence tomography; logMAR, logarithm of the minimum angle of resolution; BCVA, best-corrected visual acuity; CMT, central macular thickness; NC, nuclear cataract; PSC, posterior subcapsular cataract; CC, cortical cataract. Values are presented as number, range, percentage or mean ± standard deviation. *Independent-samples t-test, ⁺Chi-square test.

Table 3. Distribution of occult macular pathologies

Parameters	Number (percentage)
Age-Related Macular Degeneration	40 (40.0%)
Epiretinal Membrane	31 (31.0%)
Vitreomacular Traction	11 (11.0%)
Lamellar Macular Hole	8 (8.0%)
Macular Pseudohole	5 (5.0%)
Diabetic Macular Edema	5 (5.0%)

Table 4. Multivariable logistic regression analysis of patient factors predicting occult macular pathologies

Parameters	Odds Ratio (OR)	95% Confidence Interval	p
Age	**1.086**	1.055-1.118	**0.001**
Sex (female)	0.858	0.553-1.331	0.495
Systemic Comorbidities	1.214	0.688-2.142	0.504
BCVA	1.385	0.579-3.313	0.464
Grade of Cataract	0.859	0.531-1.389	0.536

BCVA, best-corrected visual acuity. Significant p-values are shown in bold.

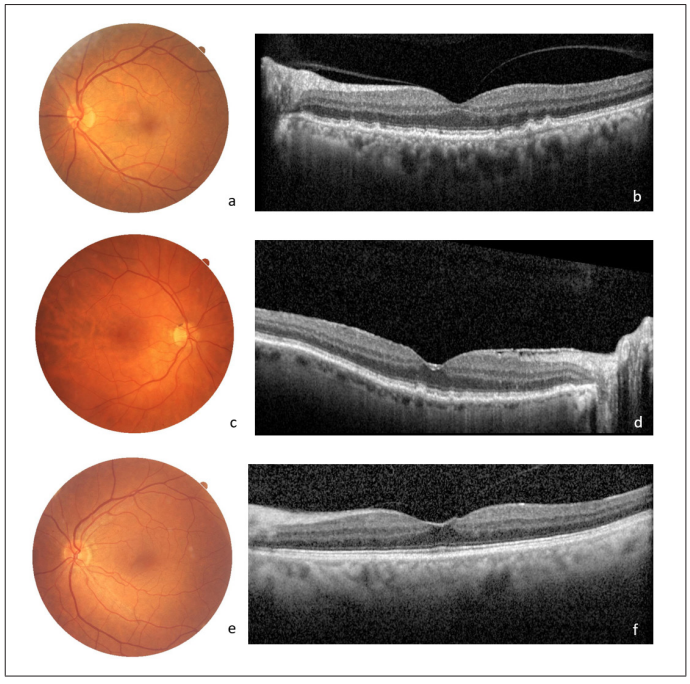

Figure 1. The fundus photographs of the three patients show no pathology in the macula **(a,c,e)**. Preoperative macular spectral-domain optical coherence tomography of cataract patients with a normal fundus biomicroscopic examination depicting **(b)** vitreomacular adhesion, and age-related macular degeneration, **(d)** mild epiretinal membrane, **(f)** vitreomacular traction syndrome.

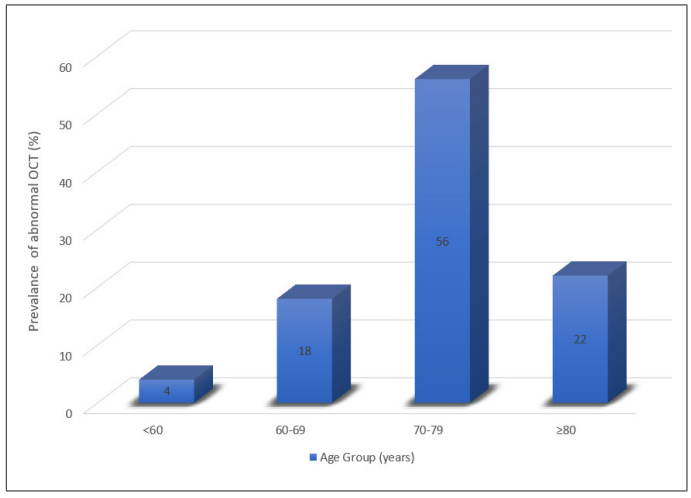

Figure 2. Distribution of patients with abnormal macular optical coherence tomography (OCT) findings prior to cataract surgery, according to age.

(p=0.001). Each 1-year increase in age was associated with a 1.086-fold increase in the odds of having an abnormal OCT finding, with a 95% CI of 1.055–1.118 (Table 4). Sex, grade of cataract, BCVA, and systemic comorbidities were found to have no statistically significant effect on the probability of being included in the abnormal OCT group (p>0.05 for all).

After excluding 2 patients whose surgery was cancelled, in 98 patients with occult macular pathology who underwent cataract surgery as planned, the preoperative BCVA value increased from 0.67±0.24 logMAR to 0.15±0.1 logMAR (at 1 month postoperatively). The difference between preoperative and postoperative BCVA was statistically significant (P=0.01). However, there was no significant difference in postoperative BCVA values between the normal OCT and abnormal OCT groups (P=0.18). When the pathologies comprising the abnormal OCT group were evaluated separately, none of the patients had visual acuity worse than 0.30 logMAR.

Discussion

In the current study, we found that pre-cataract surgery evaluation using fundoscopic examination alone may miss occult macular pathology detectable by OCT in approximately 1 in 10 eyes. Some of these pathologies are likely to affect visual outcomes and may necessitate modifications in the planning of cataract surgery. Additionally, older age was found to be the only significant predictor affecting the results of this study.

Pathologies detectable by OCT are important for anticipating final visual acuity and documenting preoperative retinal status for postoperative follow-up of potential retinal complications. Furthermore, given the high sensitivity of multifocal intraocular lenses to ocular comorbidities, reli-

able assessment of macular function with OCT has become increasingly important (23). In cases of significant macular pathology, the surgeon may wish to consult a retina specialist before surgery. This consultation can help in controlling the retinal pathology before surgery, identifying additional interventions that can be performed during surgery (such as intravitreal injections), deciding on combined surgery, and making decisions such as postponing or canceling the surgery. Weill et al. (16) consulted retinal specialists with 34 patients with occult macular pathology, and their recommendations were as follows: Surgical plan remained unchanged for 15 patients, preoperative treatment was required for 11 patients, combined surgery was performed in 4 patients, surgery was cancelled in 3 patients, and intraoperative intravitreal injection was performed in 1 patient. In our study, in line with the recommendations of retinal specialists, intravitreal injection was planned for two patients and surgeries was postponed. None of the patients required combined surgery. Reports from different geographical regions and socioeconomic populations have indicated the usefulness of OCT prior to cataract surgery (14,24). In a systematic review analyzing population-based studies reporting postoperative visual outcomes showed that visual outcomes were related to country income levels, with ocular comorbidities being a significant contributing factor (4). These findings underscore the need for OCT evaluation in centers such as secondary-level public hospitals in developing countries and smaller settlements in our country, where phacoemulsification surgery is performed relatively intensively. However, the potential burden on healthcare systems must also be considered.

Reported prevalence of occult macular pathologies in the literature ranges from 4% to 42% (14-20). One reason for this wide variation is the lack of standardization in defining macular pathology across studies. in a study evaluating 174 eyes, Kowallick et al. (15) reported the highest prevalence in the literature (42.5%). This elevated rate is thought to be due to the classification of physiological vitreous changes as abnormal OCT findings. In contrast, in most studies, including ours, vitreous opacities were considered an exclusion criterion. Another factor contributing to the differences in reported rates is the use of OCT devices with varying resolutions, which can affect the sensitivity for detecting macular pathologies (25). Additionally, DME accounted for 5% of eyes with occult macular pathology in our study. Some macular pathologies may be influenced by demographic differences, including the prevalence of systemic comorbidities and the availability of treatment (26). Therefore, population health and treatment factors may also have contributed to the variability in reported rates of occult macular pathologies.

Pinto et al. (27) evaluated 952 eyes of 614 cataract patients with no abnormalities detected on fundoscopic examination and reported occult macular pathologies identified only by OCT in 4.9% of the eyes. The detected pathologies included ERM in 31 eyes (3.3%), AMD in 7 eyes (0.7%), intraretinal cysts in 4 eyes (0.4%), lamellar macular holes in 4 eyes (0.4%), and full-thickness macular hole in 1 eye (0.1%). They also reported that advanced age was a risk factor for abnormal OCT findings. In a study involving Chinese patients with cataract, Huang et al. (28) detected occult macular pathologies using OCT in 25% of 1176 eyes, with the most common being ERM (44.2%), followed by myopic atrophy (20.7%), and dome-shaped macula in eyes with degenerative myopia (10.8%). Myopia, hypertension, and diabetes mellitus were reported as risk factors for abnormal OCT findings. Klein et al. (24) reported a 13.2% prevalence of OCT-identified occult macular pathologies in 265 eyes. The most common three pathologies were AMD in 15 (5.6%) patients, ERM in 11 (4.1%) patients, and VMT in 1 (0.03%) patient. Male sex, smoking, and cardiovascular diseases have been reported to be associated with abnormal OCT findings. Icoz et al. (20) recently reported the first prevalence study from Turkey. Occult macular pathologies detectable only by OCT were identified in 38 of 271 eyes (14.0%). These included epiretinal membrane in 15 eyes (39.4%), AMD in 10 eyes (26.3%), VMT in eight eyes (21.0%), lamellar macular hole in two eyes (5.2%), full-thickness macular hole in one eye (2.6%), and intraretinal cyst with photoreceptor layer damage in one eye (2.6%).

In this study, we contribute to the existing literature by providing data from a larger national patient cohort. Among 1091 cataract patients, occult macular pathologies detectable only by OCT were identified in 100 eyes (9.2%). These included AMD in 40 patients (40%), ERM in 31 (31%), VMT in 11 (11%), lamellar macular hole in 8 (8%), macular pseudohole in 5 (5%), and DME in 5 (5%). The three most common pathologies, AMD, ERM, and VMT, were consistent with the findings of Icoz et al. (20). Our results support that the prevalence of abnormal macular OCT findings increases with age. Similarly, previous studies have also consistently reported that the most frequently identified risk factor is advanced age (17,19,27). However, several risk factors, including male sex, systemic hypertension, diabetes mellitus, smoking, cardiovascular disease, and myopia, have been reported in the literature (17,24,28). However, most of these studies did not employ multivariable analyses to adjust for potential confounding factors.

In the current study, the most common occult macular pathology was AMD, observed in 40 patients (40%). In a previous study, AMD was detected in 10.2% of 98 eyes by OCT, and no pathology was detected in the fundoscopic evaluation of six of these eyes (29). Early recognition of AMD requires clear visualization of the central retina during

fundus examination; however, this can be challenging in the presence of cataract or other media opacities. In our cohort, the grade of cataract was not severe enough to interfere with biomicroscopic fundus examination of the central retina. Mature cataracts and other media opacities that could hinder fundus examination were among the exclusion criteria. Current evidence indicates that cataract surgery does not have a negative effect on AMD progression (30,31). Nevertheless, because AMD is a progressive disease, patients should be reminded of the importance of regular follow-up.

In the present study, the second most common occult macular pathology was ERM, observed in 31 patients (31%). It has been reported that ERM is more common in individuals over the age of 70 (32,33). Consistently, the mean age of patients with ERM in our cohort was 74.2±7.3 years. It is known that ERM may be overlooked during biomicroscopic examination but can be readily detected by OCT (34). Although ERMs do not have a significant effect on visual prognosis at this stage, it has been reported that visual outcomes may be affected due to membrane rupture or macular edema in patients with ERMs after cataract surgery (35,36). If the ERM detected on preoperative OCT is likely to compromise visual prognosis or quality, a combined surgical approach may be considered.

The third most frequent occult macular pathology in our cohort was VMT, observed in 11 patients (11%). Even when preoperative fundoscopy reveals no notable findings, it remains important to consider the potential for postoperative retinal pathologies related to VMT, to establish appropriate follow-up intervals, and to ensure patient awareness. Pathologies less frequently observed in the current study (lamellar macular hole, macular pseudohole, and DME) may also affect postoperative visual prognosis. Identifying these conditions preoperatively allows for more accurate prediction of postoperative outcomes and may influence the timing of surgery or the need for additional interventions.

The current study has some limitations. Its single-center, retrospective design restricts the generalizability of the findings to the broader population. One contributing factor to this limitation is that only patients in whom the posterior segment could be clearly visualized on fundoscopy, despite cataract severity, were included. Nevertheless, as the largest series reported from our country, the study provides valuable insights. The experience of the physician performing the preoperative fundoscopic examination is crucial in the detection of occult macular pathologies. Because our study had a retrospective design, preoperative fundoscopic examinations could not be performed by independent observers, in contrast to OCT assessments. Inter-observer reliability analyses could not be performed. However, preoperative evaluations of all patients were performed by experienced surgeons. Another limitation is the lack of evaluation regarding which occult macular pathologies have a measurable impact on postoperative visual acuity. We lacked data regarding postoperative follow-up of occult macular pathologies. Long-term follow-up of these patients will contribute to highlighting the importance of this issue. A common limitation in the literature is the absence of standardized imaging and comparison across different OCT devices. To enhance the reliability of the findings, future studies with multicenter design, larger sample sizes, inclusion of additional variables, and standardized protocols are warranted.

Conclusion

In conclusion, in the largest patient series reported from our country, the rate of occult macular pathology in the OCT examination performed before cataract surgery was found to be 9.2%. In other words, relying solely on fundoscopy would result in overlooking approximately 1 in 10 patients with occult pathologies. In this context, our study draws attention to the necessity of OCT screening prior to cataract surgery. Patients with abnormal macular OCT findings were significantly older. If selective screening is considered, priority should be given to individuals aged 70 years and above as a high-risk group. Furthermore, preoperative macular OCT screening enables surgeons to more accurately anticipate visual prognosis and provide more objective patient counseling. However, preoperative OCT may not be suitable for all patients, especially if cost is a significant concern. This is because the incidence of occult macular pathology in our series was less than 10%, and these pathologies did not significantly affect postoperative visual acuity. It may play a more critical role in evaluating the suitability of multifocal intraocular lens.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of Gulhane Faculty of Medicine, Health Sciences University (Date: 30.09.2025, Number: 2025-413).

Informed Consent: Before all procedures, patients were given detailed information about the procedure and their consent was obtained.

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Original Article

Selection Criteria For Ophthalmic Surgeons in Turkish Society: Artificial Intelligence Supported Survey Study

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Abstract

Objectives: The objective of the study was to evaluate the criteria that play a role in the selection of ophthalmic surgeons in the Turkish society and to compare the choices of 662 individuals who are healthcare professionals (Group-1) and 517 non-healthcare professionals (Group-2) as well as different demographic subgroups.

Methods: A total of 1,179 subjects participated in the online survey between March-June 2024. After collecting demographic data, the subjects were asked to select an eye surgeon among six representative images prepared by the artificial intelligence software with three questions. These three questions first asked for age and gender, then included academic title in the selection. Lastly, age was kept constant.

Results: The mean age of the participants was 44.85±12.94 (18-80) years and the M/F ratio was 0.53. In the first question, the preference for middle-aged male surgeons was the highest with 349 (52.7%) in Group-1 and 215 (41.6%) in Group-2 (p≤0.001). In the second question, the highest preferences were for 'Associate Professor' middle-aged male surgeon with 271 (40.9%) in Group-1 and 'Professor' older aged male surgeon with 155 (30%) in Group-2 (p≤0.001). In the last question, the highest preferences were 'Associate Professor' male surgeon with 205 (31%) in Group-1 and 'Professor' male surgeon with 188 (36.4%) in Group-2 (p≤0.001).

Conclusion: The selection of ophthalmic surgeon is predominantly male and middle-aged, though this rate was higher in Group-1. It is also evident that academic title has a significant effect on the selection and alters the distribution. This effect is more pronounced in Group-2, among female and below the mean age participants. Although the predominance of male surgeons persists, it was observed that female and above the mean age participants were more inclined to select a female surgeon.

Keywords: Academic title, age, gender, healthcare professionals, ophthalmic surgeon selection, society

Introduction

The growing awareness and involvement of patients in healthcare decision-making processes has led to an increased emphasis on the selection of a suitable surgeon for elective surgical procedures. This decision is of particular significance due to the potential irreversible outcomes and the rise in patient expectations.

Patients consider a variety of factors when making this decision, including personal attributes such as age and gender of the surgeon, as well as clinical attributes such as educational background, surgical experience, board certification, academic title, reputation, and non-clinical factors such as cost of surgery, home-to-clinic distance, health insurance, and ease of scheduling (1–6). It is a highly complex process, involving the evaluation of all these factors. In the modern age, the influence of social media should not be underestimated and there are studies in the literature that examine its impact (2,4,6).

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It is important to note that this selection process may also differ between patients. Various factors related to the patients, including age group, gender, educational level, social media usage, region of residence and profession can influence patients' expectations and, consequently, their selection of a surgeon. The extant literature contains a paucity of studies that examine the relationship between demographic data and surgeon choices (2,7,8).

Despite the existence of studies in various specialities, including orthopaedics and plastic surgery, there is an absence of similar research in ophthalmology. The objective of the present study was to evaluate the criteria that play a role in the selection of ophthalmic surgeons in the society and to compare the choices of individuals who are healthcare professionals and non-healthcare professionals. In the present study, a departure from the usual approach of survey studies in the literature was employed. Rather than focusing on the significance of the criteria alone, an attempt was made to address the impact of the surgeon's age, gender and academic title on the decision-making process in a more comprehensive manner. Additionally, the choices of various demographic subgroups were analysed to assess the impact of these demographic characteristics on the selection.

Methods

The survey study was approved by the institutional ethics committee of Ege University (14.12.2023 / 23-12T/50) and conducted according to Declaration of Helsinki. An online survey was prepared using Google Forms for the purpose of data collection. All participants provided electronic informed consent prior to accessing the anonymous survey. The online survey was carried out on a voluntary and anonymous basis by participants from across Turkiye between March and June 2024. Responses were kept confidential. Participants under the age of 18 were excluded from the study.

At the beginning of the survey, participants were requested to provide their demoraphic data such as age, gender, educational level, social media use, the number of social media platforms they used, their region of residence, and occupation if they are healthcare professionals (Table 1).

In the second phase of the survey, participants were tasked with answering three questions in the assumption that they had to undergo elective ocular surgery and selecting one of six images of representative surgeons. These images were created using Midjourney, an artificial intelligence programme that generates images from textual descriptions. The images were designed to exhibit similar facial types, skin tones, hairstyles and eye colours, while also highlighting the age difference between the surgeons. For this purpose, a total of six images were created in younger, middle and older age groups, with one male and one female in each group. Initially, the young male and female surgeon images were generated, and the subsequent images for middle-aged and older surgeons were derived from these, keeping the facial types, skin tones, hairstyles, eye colors, and facial expressions consistent, while only adjusting the apparent age in the prompts. All participants were presented with the images in the same fixed order, without randomization, to maintain a consistent presentation across the survey.

Table 1. Demographic data obtained from the participants in the survey

- Age
- Gender (Male or Female)
- Educational level
  - Iliterate
  - Literate but not graduated from a school
  - Primary school
  - Secondary school or equivalent vocational school
  - Primary education
  - High school or equivalent vocational school
  - College or faculty
  - Master's degree and above
- Region of residence
  - Metropolitan / City centre
  - County town
  - Countryside / Village
- Social media usage (Yes or No)
- Number of social media platforms used (0-4 or >4)
- If a health professional, his/her occupation
  - Medical doctor
  - Dentist
  - Pharmacist
  - Nurse
  - Physiotherapist
  - Dietitian
  - Technician
  - Medical secretary
  - Others

In the first question, the participants were asked to select their preferred surgeon according to their age and gender (Fig. 1). In the second question, the criteria were expanded to include the academic title. The surgeons represented in the images from the younger age group were designated as 'Specialists' and those from the middle age group as 'Associate Professors', while the surgeons from the older age group were titled 'Professors' (Fig. 2). The aim here is to analyse the modifying effect of academic title on the participants' choices. In the third question, the age group was kept constant and the participants were asked to choose their preferred surgeon only according to gender and academic title (Fig. 3). For this reason, only representative surgeon images of both genders belonging to the middle age group were used in this question.

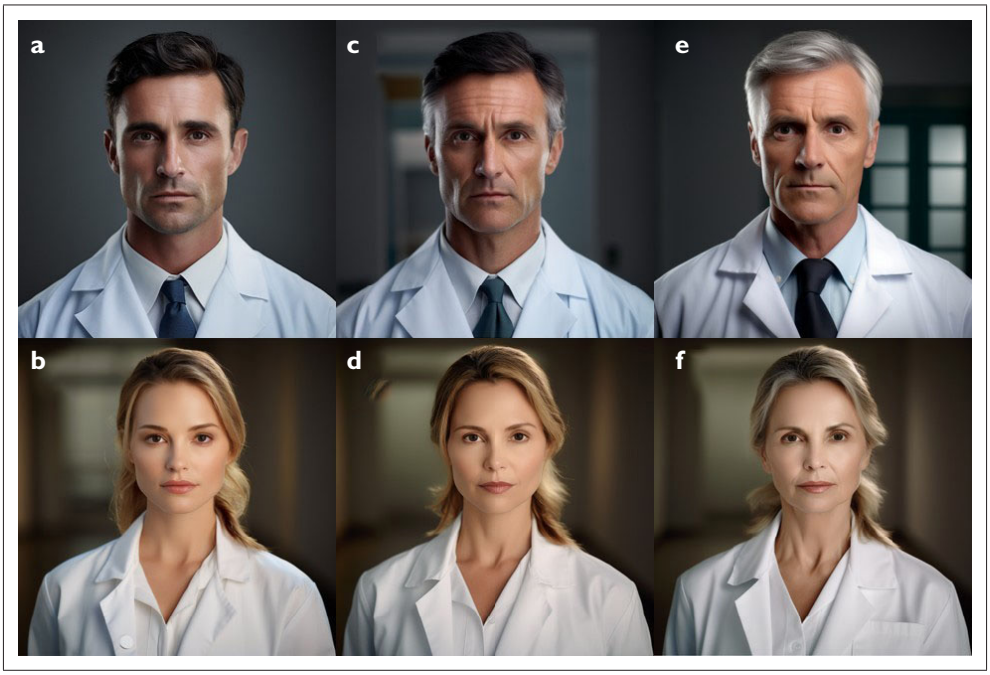

Figure 1. Representative surgeon images generated by artificial intelligence and used in the first surgeon selection question. In this question, participants were asked to select surgeons based on age and gender. **a)** Younger male surgeon. **b)** Younger female surgeon. **c)** Middle-aged male surgeon. **d)** Middle-aged female surgeon. **e)** Older male surgeon. **f)** Older female surgeon.

The data obtained from the survey results were analysed, and the surgeon choices of the two groups of healthcare professionals and non-healthcare professionals were compared. All participants were also grouped according to their demographic data, including age, gender, education level, social media usage, and region of residence. The surgeon choices of these different demographic subgroups were also compared.

Statistical analysis was performed using IBM SPSS Statistics Software (IBM, Illinois, USA). In the present study, the Wilcoxon rank sum test was used to analyse continuous variables, whilst the Pearson Chi-square test and Fisher's exact test were used to analyse categorical variables. The significance levels of the relationships and differences between variables were determined by these tests, and $P<0.05$ was accepted as the statistical significance level.

Results

A total of 1,179 subjects participated in the online survey between March and June 2024. Demographic data of all participants are presented in Table 2. The surgeon selection rates of all participants are displayed in Table 3.

Among the all participants, 662 (56.1%) were healthcare professionals (Group 1) and 517 (43.9%) were non-healthcare (Group 2) professionals. Demographic data of both groups are presented in Table 2. The occupational distribution of health professionals was as follows: 507 (76.6%) medical doctors, 65 (9.8%) nurses, 35 (5.3%) pharmacists, 28 (4.2%) dentists, 15 (2.3%) technicians, 4 (0.6%) medical secretaries, 1 (0.2%) dieticians and 7 (1.1%) other health professionals. The surgeon selection rates of both groups are displayed in Table 3.

In addition, all participants were grouped according to gender as male (n=410, 34.8%) and female (n=769, 65.2%), and their choice of surgeon was analysed. The surgeon selection rates for male and female participants are shown in Table 4.

Participants were grouped as below (Group A, n=533) and above (Group B, n=646) the mean age, and the surgeon choices of these groups were analysed. The surgeon selection rates of participants below (Group A) and above (Group B) the average age can be seen in Table 5.

Participants were also grouped as social media users (n=1130) and non-users (n=49). The surgeon selection rates of social media users and non-users are given in Table 6. Among social media users, surgeon selections of single social media platform users (n=343) and multiple social media platform users (n=787) were compared. The surgeon selection rates for single social media platform users and multiple social media platform users are shown in Table 7.

Following a comprehensive analysis of the relationship between the region of residence and the responses provided to the surgeon selection questions, it was observed that the calculation of significance was unable to be conducted due

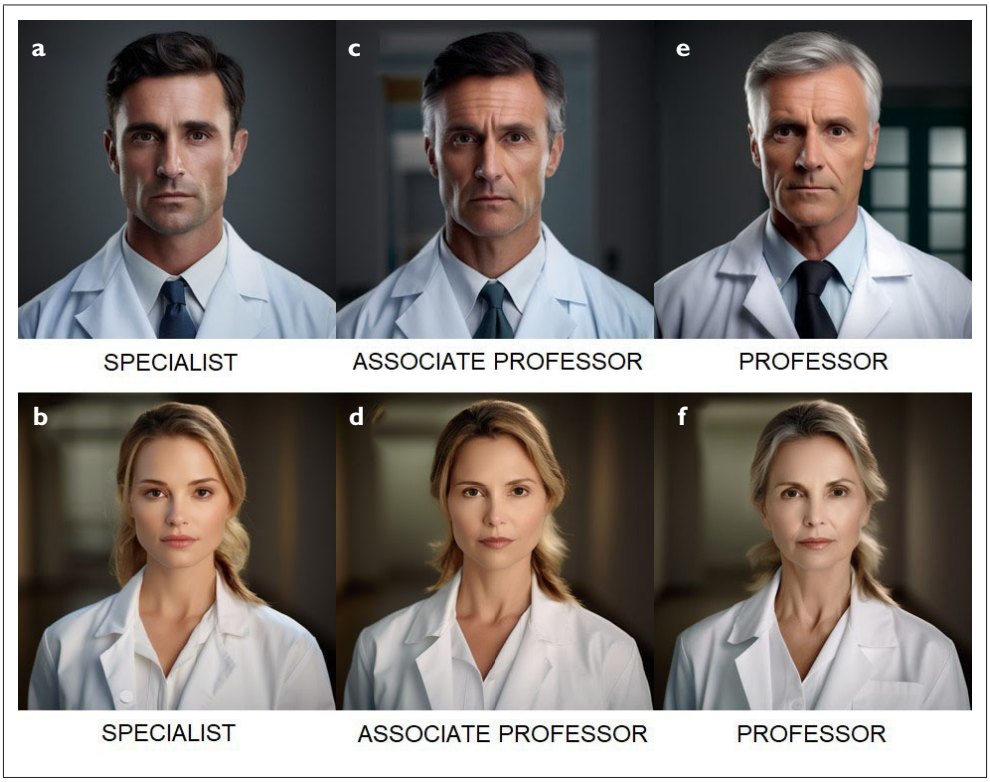

Figure 2. Representative surgeon images generated by artificial intelligence and used in the second surgeon selection question. In this question, participants were asked to select surgeons by considering their academic title in addition to age and gender. **a)** Specialist younger male surgeon. **b)** Specialist younger female surgeon. **c)** Associate professor middle-aged male surgeon. d) Associate professor middle-aged female surgeon. **e)** Professor older male surgeon. **f)** Professor older female surgeon.

to the marked differences in the size of the sample groups. However, the distribution of responses is given in Table 8.

A similar scenario was observed in the relationship between education level and surgeon choices, where significance could not be calculated due to the substantial number of groups representing education levels and the considerable variations in the sample sizes of these groups. The distribution of the responses of the education level groups to the surgeon selection questions is presented in Table 9.

Discussion

A subsequent analysis of the surgeon choices of all participants revealed that the three most preferred surgeons in the initial surgeon selection question were middle-aged male, middle-aged female and older male, respectively. With the inclusion of the academic title in the second question, it was observed that the selection rates of middle-aged surgeons with the title of associate professor decreased, whereas the selection rates of older surgeons with the title of professor increased. While the associate professor middle-aged male surgeon remained the most preferred, professor older male surgeon ranked second. In the third question, where the age was kept constant as middle age, we observe that the selection rates of surgeons with the title of professor increased, and vice versa, the selection rates of surgeons with the title of associate professor decreased. In this question, the first three ranks are as follows: Professor male, associate professor male, professor female.

When we evaluate these results, it can be said that the surgeon selections of the individuals are middle-aged and mostly male surgeons. In studies that analysed the impact of surgeon age, this was found to be a relatively insignificant factor (3,4). In another study, 54% of participants did not specify their age preference, but those who did expressed a preference for surgeons within the same age group (7). A review of the literature reveals the existence of studies reporting that advanced age is associated with unfavourable surgical results in various other surgical fields (9). However, there are also studies reporting contradictory findings (10). In a study of 499,650 cataract cases in ophthalmic surgery, it was demonstrated that advanced career stage was not associated with an elevated risk of adverse surgical events (11). A minimal increased risk for dropped lens fragments and suspected endophthalmitis was observed (11). We think that the reason for the predominance of middle age here is that ophthalmic surgery is seen as a sensitive surgery by the

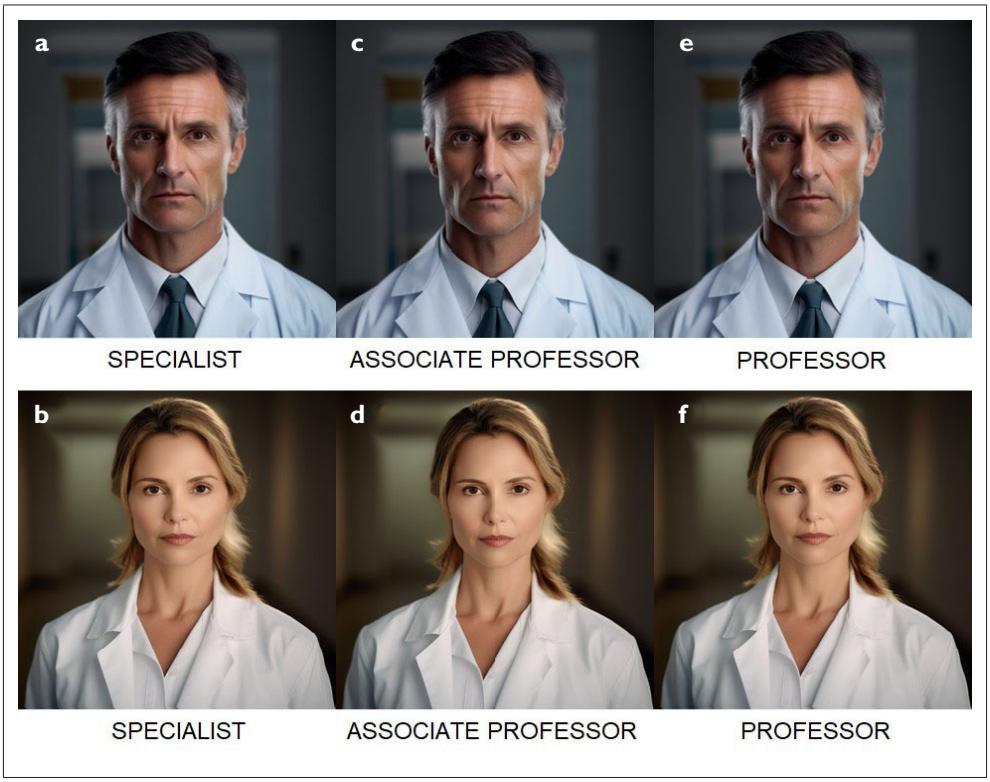

Figure 3. Representative surgeon images generated by artificial intelligence and used in the third surgeon selection question. In this question, participants were asked to choose among surgeons in the same age group by academic title and gender. **a)** Specialist male surgeon. **b)** Specialist female surgeon. c) Associate professor male surgeon. **d)** Associate professor female surgeon. **e)** Professor male surgeon. **f)** Professor female surgeon.

society and therefore middle age is seen as a safe point of surgical experience and surgical dexterity or sensitivity.

The study also observed a predominance of male surgeons, although the sample population was predominantly educated, with approximately 88% of participants having attained a college or faculty level or higher. Additionally, approximately 83% of the participants resided in metropolitan and city centres, and approximately 65% of the participants were female. Male surgeon predominance may also be related to the perspective and social structure of Turkish society. In most studies in the literature, it was reported that the participants did not have a specific surgeon gender preference (2,7,8,12).

The results also indicate that academic title has a significant impact on surgeon selection preferences, particularly when the age variable is excluded. A significant proportion of studies on surgeon selection in the literature have identified board certification, reputation and surgical experience as the most important factors (2,3,13,14). A review of the literature reveals that, in the limited number of studies that have evaluated academic position as a factor, Elmer et al. (2) found that affiliation with academia was less important than surgeon experience, board certification and years in practice. In the study conducted by Aydin et al. (6) in Türkiye, 91% of respondents characterised the academic position as important to varying degrees. However, only 48% of participants rated it as important or very important. The findings of this study are more aligned with the results of our own research. In our study, the impact of academic titles on surgeon selections can be attributed to their influence in Turkish society. While a higher academic title may represent a high level of knowledge and interest in the relevant medical field, it is not the sole determinant of surgical competence. However, within the Turkish social structure, a higher academic title may be perceived as a symbol of reputation, experience, competence and knowledge in terms of surgery.

When the surgeon choices of the participants who were healthcare professionals (Group 1) and non-healthcare professionals (Group 2) were compared, there was a significant difference between the two groups in all three surgeon choice questions. In the first question, the most preferred surgeons in both groups were middle-aged male, middle-aged female and older male, respectively. This is similar to the trend in all participants, but the rates of middle-aged surgeons were higher in Group 1 than in Group 2, while the rates of younger and older surgeons were higher in Group 2 and a signif-

Table 2. Demographic data of total, healthcare professional (Group 1) and non-healthcare professional (Group 2) participants

	Total (n=1179, 100%)	Group 1 (n=662, 56.1%)	Group 2 (n=517, 43.9%)	p
Age, mean±SD (min-max), years	44.85±12.94 (18-80)	44.52±13.11 (22-72)	42.27±12.71 (18-80)	0.5
Gender, n (%)				
Male	410 (34.8)	231 (34.9)	179 (34.6)	>0.9
Female	769 (65.2)	431 (65.1)	338 (65.4)	
Educational level, n (%)				
Illiterate	0 (0.0)	0 (0.0)	0 (0.0)	Cannot be calculated
Literate	0 (0.0)	0 (0.0)	0 (0.0)	
Primary school	19 (1.6)	0 (0.0)	19 (3.7)	
Secondary school	15 (1.3)	0 (0.0)	15 (2.9)	
Primary education	6 (0.5)	0 (0.0)	6 (1.2)	
High school	108 (9.2)	3 (0.5%)	105 (20.3)	
College or faculty	470 (39.9)	199 (30.1%)	271 (52.4)	
Master's degree or above	561 (47.6)	460 (69.5%)	101 (19.5)	
Region of residence, n (%)				
Metropolitan or city centre	974 (82.6)	587 (88.7)	387 (74.6)	<0.001
County towns	178 (15.1)	67 (10.1)	111 (21.5)	
Countryside or village	27 (2.3)	8 (1.2)	19 (3.7)	
Social media usage, n (%)				
Yes	1130 (95.8)	640 (96.7)	490 (94.8)	0.1
No	49 (4.2)	22 (3.3)	27 (5.2)	
Number of social media platforms used, n (%)				
None	49 (4.2)	22 (3.3)	27 (5.2)	0.2
One platform	343 (29.1)	190 (28.7)	153 (29.6)	
Two platforms	442 (37.5)	250 (37.8)	192 (37.1)	
Three platforms	299 (25.4)	179 (27)	120 (23.2)	
Four or more platforms	46 (3.9)	21 (3.2)	25 (4.8)	

Table 3. Surgeon selection rates of total, healthcare professional (Group 1) and non-healthcare professional (Group 2) participants

	Total (n=1179, 100%)	Group 1 (n=662, 56.1%)	Group 2 (n=517, 43.9%)	p
Surgeon selection of the first question, n (%)				
Younger male	66 (5.6)	35 (5.3)	31 (6.0)	<0.001
Younger female	70 (5.9)	21 (3.2)	49 (9.5)	
Middle-aged male	564 (47.8)	349 (52.7)	215 (41.6)	
Middle-aged female	260 (22.1)	160 (24.2)	100 (19.3)	
Older male	137 (11.6)	58 (8.8)	79 (15.3)	
Older female	82 (7.0)	39 (5.9)	43 (8.3)	
Surgeon selection of the second question, n (%)				
Specialist younger male	50 (4.2)	23 (3.5)	27 (5.2)	<0.001
Specialist younger female	55 (4.7)	26 (3.9)	29 (5.6)	
Associate professor middle-aged male	403 (34.2)	271 (40.9)	132 (25.5)	
Associate professor middle-aged female	204 (17.3)	129 (19.5)	75 (14.5)	
Professor older male	284 (24.1)	129 (19.5)	155 (30)	
Professor older female	183 (15.5)	84 (12.7)	99 (19.1)	
Surgeon selection of the third question, n (%)				
Specialist male	56 (4.7)	33 (5.0)	23 (4.4)	<0.001
Specialist female	54 (4.6)	24 (3.6)	30 (5.8)	
Associate professor male	312 (26.5)	205 (31)	107 (20.7)	
Associate professor female	171 (14.5)	113 (17.1)	58 (11.2)	
Professor male	367 (31.1)	179 (27)	188 (36.4)	
Professor female	219 (18.6)	108 (16.3)	111 (21.5)	

Table 4. Surgeon selection rates of male and female participants.

	Male Participants (n=410, 34.8%)	Female Participants (n=769, 65.2%)	p
Surgeon selection of the first question, n (%)			
Younger male	28 (6.8)	38 (4.9)	
Younger female	31 (7.6)	39 (5.1)	
Middle-aged male	219 (53.4)	345 (44.9)	<0.001
Middle-aged female	58 (14.1)	202 (26.3)	
Older male	58 (14.1)	79 (10.3)	
Older female	16 (3.9)	66 (8.6%)	
Surgeon selection of the second question, n (%)			
Specialist younger male	26 (6.3)	24 (3.1)	
Specialist younger female	21 (5.1)	34 (4.4)	
Associate professor middle-aged male	174 (42.4)	229 (29.8)	<0.001
Associate professor middle-aged female	55 (13.4)	149 (19.4)	
Professor older male	93 (22.7)	191 (24.8)	
Professor older female	41 (10)	142 (18.5)	
Surgeon selection of the third question, n (%)			
Specialist male	31 (7.6)	25 (3.3)	
Specialist female	17 (4.1)	37 (4.8)	
Associate professor male	140 (34.1)	172 (22.4)	<0.001
Associate professor female	52 (12.7)	119 (15.5)	
Professor male	126 (30.7)	241 (31.3)	
Professor female	44 (10.7)	175 (22.8)	

icant difference was observed between the two groups in terms of selection rates. A further analysis of the results of the second question reveals a decline in the selection rates of younger surgeons who hold the title of specialist and middle-aged surgeons who hold the title of associate professor, alongside an increase in the selection rates of their older counterparts who hold the title of professor. This academic title effect, is more evident in Group 2. The surgeon with

Table 5. Surgeon selection rates of participants below (Group A) and above (Group B) the mean age

	Group A (n=533, 45.2%)	Group B (n=646, 54.8%)	p
Surgeon selection of the first question, n (%)			
Younger male	34 (6.4)	32 (5.0)	
Younger female	22 (4.1)	48 (7.4)	
Middle-aged male	280 (52.5)	284 (44)	0.007
Middle-aged female	102 (19.1)	158 (24.5)	
Older male	63 (11.8)	74 (11.5)	
Older female	32 (6.0)	50 (7.7)	
Surgeon selection of the second question, n (%)			
Specialist younger male	20 (3.8)	30 (4.6)	
Specialist younger female	20 (3.8)	35 (5.4)	
Associate professor middle-aged male	187 (35.1)	216 (33.4)	0.001
Associate professor middle-aged female	74 (13.9)	130 (20.1)	
Professor older male	155 (29.1)	129 (20)	
Professor older female	77 (14.4)	106 (16.4)	
Surgeon selection of the third question, n (%)			
Specialist male	20 (3.8)	36 (5.6)	
Specialist female	13 (2.4)	41 (6.3)	
Associate professor male	131 (24.6)	181 (28)	<0.001
Associate professor female	67 (12.6)	104 (16.1)	
Professor male	209 (39.2)	158 (24.5)	
Professor female	93 (17.4)	126 (19.5)	

Table 6. Surgeon selection rates of social media users and non-users

	Social media users (n=1130, 95.8%)	Non-users (n=49, 4.2%)	p
Surgeon selection of the first question, n (%)			
Younger male	61 (5.4)	5 (10.2)	
Younger female	68 (6.0)	2 (4.1)	
Middle-aged male	537 (47.5)	27 (55.1)	0.4
Middle-aged female	252 (22.3)	8 (16.3)	
Older male	131 (11.6)	6 (12.2)	
Older female	81 (7.2)	1 (2.0)	
Surgeon selection of the second question, n (%)			
Specialist younger male	47 (4.2)	3 (6.1)	
Specialist younger female	52 (4.6)	3 (6.1)	
Associate professor middle-aged male	376 (33.3)	27 (55.1)	0.023
Associate professor middle-aged female	200 (17.7)	4 (8.2)	
Professor older male	276 (24.4)	8 (16.3)	
Professor older female	179 (15.8)	4 (8.2)	
Surgeon selection of the third question, n (%)			
Specialist male	53 (4.7)	3 (6.1)	
Specialist female	51 (4.5)	3 (6.1)	
Associate professor male	293 (25.9)	19 (38.8)	0.02
Associate professor female	168 (14.9)	3 (6.1)	
Professor male	353 (31.2)	14 (28.6)	
Professor female	212 (18.8)	7 (14.3)	

the highest rate in the second question is associate professor middle-aged male surgeon in Group 1 and professor older male surgeon in Group 2. In Group 1, it is evident that there is a smaller decrease in the proportion of middle-aged surgeons, even with the option of holding a higher academic title, and that they maintain their position in the first two

Table 7. Surgeon selection rates of single media platform users and multiple social media platform users

	Single social media platform users (n=343, 29.1%)	Multiple social media platform users (n=787, 66.7%)	p
Surgeon selection of the first question, n (%)			
Younger male	26 (7.6)	35 (4.4)	
Younger female	20 (5.8)	48 (6.1)	
Middle-aged male	155 (45.2)	382 (48.5)	0.3
Middle-aged female	83 (24.2)	169 (21.5)	
Older male	36 (10.5)	95 (12.1)	
Older female	23 (6.7)	58 (7.4)	
Surgeon selection of the second question, n (%)			
Specialist younger male	23 (6.7)	24 (3.0)	
Specialist younger female	17 (5.0)	35 (4.4)	
Associate professor middle-aged male	106 (30.9)	270 (34.3)	0.013
Associate professor middle-aged female	58 (16.9)	142 (18)	
Professor older male	73 (21.3)	203 (25.8)	
Professor older female	66 (19.2)	113 (14.4)	
Surgeon selection of the third question, n (%)			
Specialist male	20 (5.8)	33 (4.2)	
Specialist female	15 (4.4)	36 (4.6)	
Associate professor male	91 (26.5)	202 (25.7)	0.4
Associate professor female	43 (12.5)	125 (15.9)	
Professor male	102 (29.7)	251 (31.9)	
Professor female	72 (21)	140 (17.8)	

Table 8. Distribution of surgeon selection rates by participants' region of residence

	Metropolitan or City Centre (n=974, 82.6%)	County towns (n=178, 15.1%)	Countryside or village (n=27, 2.3%)
Surgeon selection of the first question, n (%)			
Younger male	55 (5.6)	11 (6.2)	0 (0)
Younger female	46 (4.7)	18 (10.1)	6 (22.2)
Middle-aged male	484 (49.7)	73 (41)	7 (25.9)
Middle-aged female	214 (22)	41 (23)	5 (18.5)
Older male	105 (10.8)	23 (12.9)	9 (33.3)
Older female	70 (7.2)	12 (6.7)	0 (0)
Surgeon selection of the second question, n (%)			
Specialist younger male	42 (4.3)	8 (4.4)	0 (0)
Specialist younger female	44 (4.5)	7 (3.9)	4 (14.8)
Associate professor middle-aged male	344 (35.3)	52 (29.2)	7 (25.9)
Associate professor middle-aged female	168 (17.2)	32 (18)	4 (14.8)
Professor older male	232 (23.8)	44 (24.7)	8 (29.6)
Professor older female	144 (14.8)	35 (19.7)	4 (14.8)
Surgeon selection of the third question, n (%)			
Specialist male	51 (5.2)	5 (2.8)	0
Specialist female	39 (4)	10 (5.6)	5 (18.5)
Associate professor male	256 (26.3)	49 (27.5)	7 (25.9)
Associate professor female	139 (14.3)	30 (16.9)	2 (7.4)
Professor male	310 (31.8)	48 (27)	9 (33.3)
Professor female	179 (18.4)	36 (20.2)	4 (14.8)

Table 9. Surgeon selection rates of education level groups

	Primary school (n=19, 1.6%)	Secondary school (n=15, 1.3%)	Primary education (n=6, 0.5%)	High school (n=108, 9.2%)	College or faculty (n=470, 39.9%)	Master's degree or above (n=561, 47.6%)
Surgeon selection of the first question, n (%)						
Younger male	2 (10.5)	0 (0)	1 (16.7)	10 (9.3)	26 (5.5)	27 (4.8)
Younger female	6 (31.6)	0 (0)	1 (16.7)	13 (12)	31 (6.6)	19 (3.4)
Middle-aged male	5 (26.3)	5 (33.3)	1 (16.7)	39 (36.1)	213 (45.3)	301 (53.7)
Middle-aged female	3 (15.8)	5 (33.3)	1 (16.7)	21 (19.4)	101 (21.5)	129 (23)
Older male	3 (15.8)	3 (20)	1 (16.7)	17 (15.7)	66 (14)	47 (8.4)
Older female	0 (0)	2 (13.3)	1 (16.7)	8 (7.4)	33 (7)	38 (6.8)
Surgeon selection of the second question, n (%)						
Specialist younger male	3 (15.8)	0 (0)	0 (0)	5 (4.6)	26 (5.5)	16 (2.9)
Specialist younger female	2 (10.5)	0 (0)	0 (0)	12 (11.1)	22 (4.7)	19 (3.4)
Associate professor middle-aged male	2 (10.5)	3 (20)	1 (16.7)	27 (25)	141 (30)	229 (40.8)
Associate professor middle-aged female	1 (5.3)	3 (20)	2 (33.3)	19 (17.6)	71 (15.1)	108 (19.3)
Professor older male	7 (36.8)	4 (26.7)	1 (16.7)	22 (20.4)	135 (28.7)	115 (20.5)
Professor older female	4 (21.1)	5 (33.3)	2 (33.3)	23 (21.3)	75 (16)	74 (13.2)
Surgeon selection of the third question, n (%)						
Specialist male	2 (10.5)	0 (0)	0 (0)	5 (4.6)	23 (4.9)	26 (4.6)
Specialist female	3 (15.8)	0 (0)	0 (0)	11 (10.2)	22 (4.7)	18 (3.2)
Associate professor male	4 (21.1)	3 (20)	1 (16.7)	23 (21.3)	105 (22.3)	176 (31.4)
Associate professor female	1 (5.3)	2 (13.3)	2 (33.3)	11 (10.2)	60 (12.8)	95 (16.9)
Professor male	5 (26.3)	6 (40)	1 (16.7)	32 (29.6)	166 (35.3)	157 (28)
Professor female	4 (21.1)	4 (26.7)	2 (33.3)	26 (24.1)	94 (20)	89 (15.9)

places. Similarly, in the third question, the highest rates are associate professor male surgeon in Group 1 and professor male surgeon in Group 2. In the third question, we observe that the effect of academic title becomes more noticeable in both groups when age is kept constant. However, while the rates of surgeons with the title of professor and the rates of surgeons with the title of associate professor are very close to each other in Group 1, the rate of surgeons with the title of associate professor is higher.

In the light of these results, we see that male dominance is observed in both groups. Although middle-aged surgeons are prioritised in both groups, the fact that the selection rate of older surgeons and the effect of academic title is higher in Group 2 compared to Group 1 suggests that the non-healtcare professional participants values years in experience and academic title more. This situation may be related to the differences in the education levels or the region of residence between the two groups, as well as the impressions of the healthcare professionals from the working environment. The impression gained from the working environment may be that some middle-aged surgeons with the title of associate professor have a higher case load and therefore are more active in terms of surgery than older surgeons with the title of professor. Consequently, the impression among healthcare professionals that surgical dexterity is superior in middle-aged surgeons may have arisen from both this factor and the younger age of the surgeon.

When the subgroup analyses were examined according to demographic data, the participants were grouped according to gender. A significant difference was observed between the responses of male and female participants in all three surgeon selection questions. In the first question, following the general trend, the three surgeons with the highest rates were middle-aged male, middle-aged female and older male, but there was a significant difference between the two groups in terms of selection rates. With the inclusion of academic title, similar to the previous scenarios, an increase was observed in the selection rates of older surgeons with higher academic titles, while conversely, a decrease was observed in the selection rates of specialist younger age and associate professor middle-aged surgeons. In the second question, the top 3 surgeons with the highest selection rates in both groups were associate professor middle-aged male, professor older male, associate professor middle-aged female, respectively, but there was a significant difference in selection rates. When age was kept constant, the effect of academic title was observed more clearly. In the last surgeon selection question, the top two surgeons selected by the male participants were associate professor male and professor male, while the top two surgeons selected by the female participants were professor male and professor female. This change in the rates due to the effect of academic title was more evident in female participants than in male participants.

A thorough analysis of the rates from the initial question reveals that both groups are predominantly comprised of middle-aged surgeons, as was the case in previous scenarios. In addition, an analysis of the rates in the three surgeon selection questions reveals that the female surgeon selection rates of female participants exceed those of male participants. Consequently, while there is a male surgeon predominance in both groups, it can be concluded that female participants exhibit a stronger tendency to select a female surgeon in comparison to male participants. As with the situation under consideration in our study, the literature also contains studies reporting that female participants tend to choose female surgeons more often than male participants (8,15).

When the participants were subgrouped as below (Group A) and above (Group B) the mean age, a significant difference in the rates was observed in all three surgeon selection questions. In the initial question, the highest selection rates in both groups were observed to be middle-aged male, middle-aged female and older male, respectively, aligning with the general trend. In the second question, which introduced the factor of academic title, the top three ranks in Group A were associate professor middle-aged male, professor older male and professor older female, while in Group B, the top three ranks were associate professor middle-aged male, associate professor middle-aged female and professor older male. In the third question, the top three ranks were professor male, associate professor male, professor female for Group A, and associate professor male, professor male, professor female for Group B.

The analysis of ratios and rankings indicates that the effect of academic title is more apparent in Group A, suggesting that younger participants value academic titles to a greater extent. Additionally, analysis of the first question's rates reveals a predominance of middle-aged surgeons in both groups, consistent with previous scenarios. It is important to note that when the ratios of the three questions are analysed, the rate of female surgeon selection by participants in Group B is higher than that of participants in Group A. This suggests that, although there remains a male predominance, participants above the average age may be more inclined to choose a female surgeon. The relationship between patient age and surgeon gender preference remains an under-researched area. A study reported that there was no significant relationship between the two (8).

A comparison was made between social media users and non-users, with the results indicating that the social media users, constituting 95.8% of the total participants, exhibited a natural alignment with the general trend across the three questions. Within the non-user group, the highest percent-

ages were observed in the middle-aged male surgeon (55% in question one) and the associate professor middle-aged male surgeon (55% in question two). However, it was noted that the proportion of older surgeons with the title of professor increased. When age was kept constant in the third question, a further increase was observed in the proportion of surgeons with the title of professor, which was similar to the general trend. While no significant difference was observed between these subgroups in the first question, a significant difference was calculated in the second and third questions. However, it should be noted that this comparison may not be entirely valid due to the size difference between the two sample groups and the small number of participants in the non-users group.

When the surgeon selection rates were analysed by dividing the participants who use social media into subgroups as single and multiple social media platform users, no significant difference was observed between the two groups in the first and third questions. However, a significant difference was observed between the rates in the second question. The surgeon rates and the change in the rates in the two groups are similar to the previous scenarios and in line with the general trend. However, in the second question, academic title may have caused a slightly higher increase in older surgeon selection rates in single platform users than in multiple platform users and a slightly higher decrease in younger surgeon selection rates in multiple platform users than in single platform users, which may have caused this significant difference. However, with these results, we believe that the exact effect of social media use and intensity of use on surgeon selection cannot be determined.

Although it is a fact that social media is having an impact on healthcare today, there are mixed results when it comes to choosing a surgeon. A study found that the surgeon's social media and online presence were significantly less important than the surgeon's background and training (2). A number of studies have indicated that online reviews and comments about the surgeon are also of limited importance (4,5). There are also studies in the literature report that advertising is not a significant factor (3,5). In the study by Aydin et al, although the majority of participants used social media, the physician's social media presence was not considered important or very important largely (6). Another study conducted in Türkiye reported that the use of social media in physician selection was low (<50%) (16).

An analysis of the relationship between the region of residence and surgeon selection reveals that the surgeon choices of the participants residing in metropolitan or city centres and the participants residing in county towns have a distribution that is largely consistent with the general trend. However, when the choices of the group residing in the countryside or village are examined, it is seen that there is a slightly different distribution. This is thought to be largely related to the small sample size of this group.

A similar situation is observed between education levels and surgeon selections. In this case, the surgeon selections of the participants in primary school, secondary school, primary education and high school education levels, where the sample size is relatively small, are slightly different from the general trend. Conversely, the surgeon choices of participants with college or faculty education level, constituting approximately 40% of the total sample, and those with a master's degree or above, constituting approximately 48%, align with the prevailing trend. The analysis of the rates of these two groups reveals that the selection rates of surgeons with the title of professor is slightly higher among the participants with college or faculty education level than that of the participants with a master's degree or above in the second and third questions. However, this situation may be related to the level of education, but it may also be due to the fact that the majority of the group with a master's degree or above is composed of medical doctors and therefore healthcare professionals.

The relationship between surgeon selection and patient education level has been the subject of only a limited number of studies in the literature. Abghari et al. (7) reported a positive trend, showing that the surgeon's medical school, residency and fellowship prestige were given greater importance with the increase in patient education level. However, they did not find a relationship between education level and years of experience preference (7). Elmer et al. (2) also reported in their study that participants with higher education levels assigned greater importance to factors related to surgeon practice than participants with lower education levels.

Global evidence suggests that cultural factors influence patients' surgeon selection beyond purely objective criteria such as age, experience, or academic title. Cultural perceptions—societal norms and expectations regarding which surgeon characteristics are considered desirable—can shape preferences for certain demographics. For instance, in a study conducted in Saudi Arabia, approximately 49.5% of participants preferred a surgeon of their own gender, with female participants showing a statistically significant preference for same-gender surgeons (17). Similarly, in a study conducted in Pakistan, about half of participants reported no gender preference; however, among those who expressed a preference, there was a strong tendency to select a gender-concordant surgeon across most surgical subspecialties, reflecting the influence of sociocultural norms on implicit gender bias (18). Implicit gender bias arises when these cultural perceptions unconsciously influence surgeon choice, even if participants do not explicitly consider gender a decisive factor. In contrast, studies from Western Europe and

North America indicate that while gender can influence patient preference, other factors such as surgeon experience, reputation, and board certification often outweigh gender in the decision-making process (2,19). In these studies, most patients who expressed a preference tended to select male surgeons, but a large proportion reported "no preference" regarding gender (7,8,12). In our study conducted in Türkiye, participants predominantly selected male and middle-aged surgeons, with academic title also significantly affecting choices. Notably, female and older participants showed a greater tendency to select female surgeons, suggesting that cultural norms and societal perceptions interact with other criteria—such as age and professional rank—in shaping surgeon preferences. This pattern highlights that, while some selection tendencies are consistent across countries (e.g., valuing experience), local cultural contexts can shift the relative importance of age, gender, and academic credentials in surgeon selection.

This study has several limitations that should be considered when interpreting the results. Although participants were recruited from various provinces across Türkiye through online access, the sample distribution was not entirely homogeneous across different geographical and socio-cultural regions. While we collected data on participants' urban versus rural residence, we did not ensure a balanced representation from all socio-cultural and regional groups in Türkiye. Similarly, there was an imbalance in education level and professional background, with highly educated healthcare professionals comprising the majority of the sample.

Also some subgroups, such as social media non-users or participants with lower education levels, had very small sample sizes, limiting the reliability and statistical power of analyses in these groups. The statistical significance of associations between surgeon selections and demographic factors such as region and education level could not be fully calculated due to highly uneven group sizes.

Moreover, participants made selections based on AI-generated images rather than real surgeons, which may not fully capture clinical experience, interpersonal skills, or other nuanced personal characteristics. In addition, the AI-generated surgeon images were presented in a fixed order, which may introduce order bias and affect participants' selections. The online survey method may also have introduced selection bias, as it primarily included individuals with internet access and interest in participation. Cultural and societal norms within Türkiye were considered, but their effects were not directly measurable and were inferred from observed patterns. Finally, interactions between multiple factors such as age, gender, and academic title were only partially analyzed, and more complex interplay may exist.

Therefore, the results should be interpreted as a reflection of general societal tendencies rather than as fully representative of the entire Turkish population. Future multi-center studies including more balanced samples from all regions and socio-cultural backgrounds of Türkiye will provide stronger evidence for the observed trends.

Conclusion

The present study is an evaluation of the selection of an ophthalmic surgeon, a practice which is becoming increasingly important in today's society. Rather than focusing on the importance of individual criteria in terms of age, gender and academic title, the study adopts a comprehensive approach. Although there have been previous studies on this subject in different medical disciplines, this is the first study in the ophthalmology literature. In the study, while comparing healthcare professionals with the general population, different demographic subgroups were also compared and the effects of individual characteristics on the selection were evaluated. In this respect, the present study differs from other research in the literature. Consequently, the selection of ophthalmic surgeon in the Turkish society is predominantly male and middle-aged. Although the predominance of male surgeons persists, it was observed that female and above the mean age participants were more inclined to select a female surgeon. It is also evident that academic title has a significant effect on the selection and alters the distribution. This effect of academic title is more pronounced among participants who are not health professionals, female and below the mean age. In order to better understand the effect of social media, region of residence and education level on surgeon choices, further studies with different designs with more homogenously distributed sample groups are needed.

Disclosure

Ethics Committee Approval: The survey study was approved by the institutional ethics committee of Ege University (Date: 14.12.2023, No: 23-12T/50)

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Original Article

Structure-Function Relationship in Patients with Glaucoma Suspect: Diagnostic Value and Changes During Follow-up

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Abstract

Objectives: To evaluate anatomical and functional changes during follow-up in eyes with glaucoma suspicion.

Methods: A total of 56 eyes of 28 patients (F/M: 21/7) who were included. Detailed ophthalmologic examination, optic coherence tomography (OCT) and visual field (VF -SITA 24-2 and 10-2) were performed at the initial and 12th month examination. Retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thicknesses, 24-2 VF global indices (MD, PSD), and 10-2 VF superior and inferior hemi-quadrant mean sensitivities (dB) were recorded. The presence of "cluster defect" was noted in both VFs.

Results: The mean age was 56.1±10.8 (34-74) years, mean IOP was 18.2±3.8 mmHg and mean cup/disc ratio (C/D) was 0.4±0.2 at the first visit. There was no significant change in mean IOP and C/D during the follow-up (p=0.655, 0.988, respectively). No significant progression was observed in OCT and VF parameters (p>0.05 for all). At the initial examination, a mild positive correlation was found between total RNFL, GCC and 24-2 MD (r=0.292, 0.316, respectively). At the 12th month, there was a moderate positive correlation between total RNFL and 24-2 MD (r=0.317) and a moderate negative correlation between total RNFL and PSD(r=-0.327). No correlation was observed between 10-2 VF superior/inferior hemi-quadrant mean sensitivity (dB) and inferior/superior RNFL and GCC in both examinations (p>0.05 for all). Cluster defect was present in 35 eyes at initial examination and in 30 eyes at 12th month.

Conclusion: There's not a single parameter that can be used to differentiate glaucoma suspects from early-stage glaucoma. VF, RNFL and GCC should all be evaluated, and longer follow-ups are necessary.

Keywords: Glaucoma suspect, retinal nerve fiber thickness, ganglion cell complex, visual field, cluster defect

Introduction

Glaucoma is a chronic, progressive optic neuropathy characterized by retinal ganglion cell loss, retinal nerve fiber layer (RNFL) thinning and visual field deterioration, and is one of the most common causes of permanent vision loss worldwide (1). In clinical practice, cases considered to be at increased risk for glaucoma and/or who may have early-stage disease but do not meet a clinical threshold for diagnosis are classified as "glaucoma suspect" (2). The European Glaucoma Society (EGS) guidelines defined glaucoma suspect as normal/high intraocular pressure (IOP) with at least one of the following parameters: Suspicious optic disc appearance, suspicious nerve fiber layer thickness, suspicious glaucomatous damage in the visual field, strong family history (3). In the United States, the prevalence of glaucoma suspect is ranging from 4.5% to 20% in population over the age of 65 and is significantly higher than the prevalence of true glauco-

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ma (4,5). In brief, the glaucoma suspect group represents a large population of patients in whom the differential diagnosis should be done as early as possible to initiate the treatment if necessary to prevent permanent visual loss and at the same time to prevent unnecessary visits and medications for patients who actually don't need it, therefore reduce the burden on healthcare system.

For many years, traditional glaucoma diagnosis and follow-up were performed by evaluating the anatomical damage in the optic nerve and peripapillary RNFL with optic coherence tomography (OCT), and the functional reflection of this damage with standard automated perimetry (6). Glaucomatous defects affecting the central 10-degree visual field (VF) were thought to occur only in the advanced stages of glaucoma. However, especially in the last decade, it has been documented that the macular ganglion cell complex (GCC), which includes the three innermost retinal layers (GCL=ganglion cell layer; IPL=inner plexiform layer; RNFL=retinal nerve fiber layer), is involved at early stage and that visual field sensitivity loss in the macular region is no longer considered as advanced sign of glaucoma (7–9).It is even claimed that macular GCC and 10-2 VF defects may sometimes be the only symptoms of early glaucoma and may even occur in glaucoma suspect (10–12).

The structure-function relationship is an important point in glaucoma research and the unclear nature of this relationship is still being discussed. In the literature, there are studies reporting that central functional defects correlate with GCC defects, and 24-2 VF defects correlate with RNFL defects (13–15).

In light of this information, the present study aims to report the first-year outcomes of patients suspected of glaucoma who were followed up to evaluate anatomical and functional changes during follow-up and to determine the most reliable parameter for early glaucoma diagnosis.

Methods

Patients who were followed up with primary open angle glaucoma suspect diagnosis at Ege University Department of Ophthalmology were included in the study. The diagnosis was made according to the criteria defined in the ESG guidelines by the two glaucoma specialists (MEB and SG). Inclusion criteria were defined as to have regular follow-up visits and reliable visual field tests. Exclusion criteria were defined as being under 18 years of age, using any anti-glaucomatous medication, presence of other ocular, systemic, or neurological pathology that may affect the results, history of any previous ocular surgery except routine cataract surgery and intraocular lens implantation, media opacity that deteriorate the results and refractive error that spherical equivalent higher than +/-5.0 diopters.

All patients underwent a detailed ophthalmological examination, including best-corrected visual acuity (BCVA), biomicroscopic anterior segment evaluation and posterior segment examination using 90 D lens, IOP measurements using Goldmann applanation tonometer at the initial visit and at 12th months. RNFL (total, superior, inferior, nasal, temporal) and GCC (total, superior, inferior) measurements were taken by the same technician with 1050 nm wavelength, 100 kHz A-scan rate, and 8-µm axial resolution OCT (Swept Source OCT Triton, Topcon, Japan) after pharmacological dilation in both visits. GCC scan covered a 6x6 mm area centered on the fovea. Images with low signal index (signal strength density <41) and decentration problems were excluded. SITA (Swedish Interactive Threshold Algorithm) Standard 24-2 VF and 10-2 VF tests were performed in both visits via Humphrey Field Analyzer II, model 750 (Zeiss Humphrey Systems, Dublin, CA) using the same stimulus and spot size (Goldmann size III, white) and background luminance of 31.5 ASB with the appropriate correction of refractive error. VF reliability criteria were set as less than 10% false-positive and false-negative ratio and less than 10% loss of fixation, to have a data with good reliability. Global VF indices (MD-Mean Deviation and PSD-Pattern Standard Deviation) in 24-2 VF and arithmetic means of threshold values (differential light sensitivity) (dB) in 10-2 VF were recorded. Superior and inferior hemi-quadrant mean sensitivities were calculated as the arithmetic mean of 26 different dB measurements in the corresponding hemi-quadrant.

In both VF tests, the presence of a "cluster defect" in the pattern deviation map was investigated. Cluster defect was defined according to literature as a p value equal to or worse than 5%, 5%, 1% or 5%, 2%, 2% at 3 consecutive points (16,17).

Correlation between the corresponding VF and OCT data (total RNFL and GCC vs SITA 24-2 MD and PSD, superior RNFL and GCC vs inferior 10-2 dB, and vice versa) at the initial and 12th month visits, the presence of progression in clinical follow-up, and also the change in the cluster defect ratio were investigated.

Statistical analysis was performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) package program. Numerical data were summarized with mean, standard deviation, median, minimum, and maximum values. In pairwise comparisons, the T-test was used for parametric variables, the Mann-Whitney U test was used for nonparametric variables, and in comparisons involving three or more variables, ANOVA was used for parametric variables and the Kruskal-Wallis-H test was used for nonparametric variables. Pearson Correlation Analysis for parametric vari-

ables and Spearman Correlation Analysis for non-parametric variables were performed. A value of $p<0.05$ was considered as statistically significant. This prospective, cross-sectional study was conducted in accordance with the Principles of the Declaration of Helsinki with the approval of the Ege University Faculty of Medicine Ethics Committee. Written informed consent was obtained from all participants.

Results

A total of 56 eyes of 28 patients (21 female and 7 male) with a mean age of 56.1±10.9 years were included in the study. According to the EGS guidelines, the percentages of eyes meeting each diagnostic criterion are shown in Figure 1. The mean IOP at the initial visit was 18.2±3.8 mmHg and cup/disc ratio was 0.4±0.2, there was no statistically significant change during the follow-up (16.8±3.1 mmHg and 0.4±0.2 at 12th month) (p=0.655, 0.988, respectively). The initial and 12th month mean RNFL, GCC thicknesses, 24-2 VF MD and PSD values and 10-2 VF mean sensitivities are summarized in Table 1 and no significant progression was found (p>0.05 for all).

At the initial examination, a mild positive correlation was found between total RNFL, GCC and 24-2 MD (mean -3.43±3.7). There was a moderate positive correlation between total RNFL and 24-2 MD (mean -4.01±3.5) and a moderate negative correlation between total RNFL and PSD (mean 3.34±2.8) at the 12th month examination (Table 2).

No correlation was observed between 10-2 VF superior/inferior hemi-quadrant mean sensitivity (dB) and inferior/superior RNFL and GCC at the initial (Table 3) and 12th month examination (Table 4).

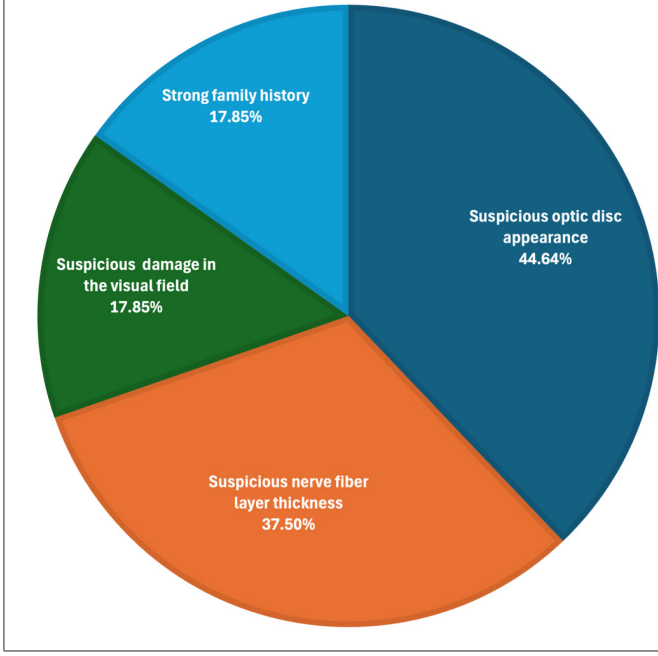

Figure 1. Distribution graph showing the percentage of each EDS diagnostic criterion met across eyes (total of 56 eyes).

Cluster defect was present in 4 eyes (7.14 %) only in 10-2 VF, 24 eyes (42.86 %) only in 24-2 VF, and 7 eyes (12.50 %) in both VF tests for a total of 35 eyes (62.5%) at initial examination. At the final examination, it was observed in 3 eyes (5.36%) only in 10-2 VF, 16 eyes (28.57 %) only in 24-2 VF, and 11 eyes (19.64 %) in both VF tests, for a total of 30 eyes (53.57%) (Table 5).

Table 1. The initial and 12th month mean OCT and VF parameters

	The initial examination	The 12th month examination	p
RNFL			
Total	100.88±13.3	101.71±18.9	0.642
Superior	120.86±20.2	121.27±21.9	0.052
Inferior	130.84±22.6	129.50±23.0	0.765
Nasal	82.50±11.6	81.48±12.2	0.186
Temporal	70.39±15.9	69.25±15.1	0.075
GCC			
Total	101.34±11.7	101.25±11.9	0.792
Superior	101.0±12.1	101.29±12.2	0.843
Inferior	101.79±11.8	101.48±12.2	0.941
24-2 VF			
MD	-3.43±3.7	-4.01±3.5	0.228
PSD	3.39±2.5	3.34±2.8	0.987
10-2 VF			
Superior hemi-quadrant dB	30.72±2.2	29.86±3.2	0.203
Inferior hemi-quadrant dB	30.95±2.6	30.43±2.8	0.229

Table 2. Correlation between OCT and GA parameters at initial examination and 12th month.

	The initial examination				The 12th month examination			
	RNFL	**GCC**	**MD**	**PSD**	**RNFL**	**GCC**	**MD**	**PSD**
RNFL								
p value	-	<0.001	0.029	0.472	-	<0.001	0.017	0.014
Correlation Coefficient		0.686	0.292	-0.098		0.694	0.317	-0.327
GCC								
p value	<0.001	-	0.018	0.250	<0.001	-	0.510	0.347
Correlation Coefficient	0.686		0.316	-0.156	0.694		0.090	-0.128

* p value is significant at the 0.05 level

Table 3. Correlation between OCT and 10-2 VF parameters at the initial examination

	RNFL Superior	**RNFL Inferior**	**GCC Superior**	**GCC Inferior**	**10-2 Inferior**	**10-2 Superior**
RNFL Superior						
p value	-	-	0.001	-	0.394	-
Correlation Coefficient			0.428		0.116	
RNFL Inferior						
p value	-	-	-	<0.0001	-	0.116
Correlation Coefficient				0.498		0.212
GCC Superior						
p value	0.001	-	-	-	0.577	-
Correlation Coefficient	0.428				0.076	
GCC Inferior						
p value	-	<0.0001	-	-	-	0.925
Correlation Coefficient		0.498				-0.013
10-2 Inferior						
p value	0.394	-	0.577	-	-	-
Correlation Coefficient	0.116		0.076			
10-2 Superior						
p value	-	0.116	-	0.925	-	-
Correlation Coefficient		0.212		-0.013		

Discussion

This study presents the first-year results of patients followed up for "glaucoma suspect" and found a mild positive correlation between total RNFL, GCC, and 24-2 VF (MD) at the initial examination; a moderately positive correlation between total RNFL and MD; and a moderately negative correlation between total RNFL and PSD at 12th months.

The correlation between RNFL and MD has been reported in the literature before, and our study is consistent with the literature. In this study, a correlation between GCC and MD was also detected at the initial examination, but it did not persist in the 12th month. Teixeira et al. (18) found a strong correlation between total, superior, and inferior GCC and 24-2 VF MD and PSD. Similar results were reported in another study by Kim et al. (19). The authors suggest that the structure-function relationship of GCC and VF is similar to that of RNFL and VF. They also indicate that GCC has the same diagnostic potential as RNFL in early, moderate, and advanced glaucoma.

Cho et al. (20) investigated the relationship between mean sensitivity (MS) (both dB and 1/Lambert) in 24-2 VF and GCC; and found correlations between MS and corresponding GCC thickness for total, superior, and inferior hemi-quadrants (for dB, r=0.444, 0.370, and 0.528, respectively) and emphasized that these results were not different from the correlation between RNFL and 24-2 VF. There are many studies in the literature investigating the correlation between these parameters, and the most recently, 2023, Dhabarde et al. (21) underlined the correlation and even found that GCC was a higher diagnostic parameter in the diagnosis of early glaucoma, although it was not statistically significant.

We attribute our result to the fact that, unlike other studies, we evaluated only glaucoma suspect patients in

Table 4. Correlation between OCT and 10-2 GA parameters at the 12th months visit

	RNFL Superior	RNFL Inferior	GCC Superior	GCC Inferior	10-2 Inferior	10-2 Superior
RNFL Superior						
p value	-	-	0.002	-	0.351	-
Correlation Coefficient			0.409		0.127	
RNFL Inferior						
p value	-	-	-	<0.001	-	0.191
Correlation Coefficient				0.588		0.177
GCC Superior						
p value	0.002	-	-	-	0.806	-
Correlation Coefficient	0.409				0.034	
GCC Inferior						
p value	-	<0.001	-	-	-	0.868
Correlation Coefficient		0.588				0.023
10-2 Inferior						
p value	0.351	-	0.806	-	-	-
Correlation Coefficient	0.127		0.034			
10-2 Superior						
p value	-	0.191	-	0.868	-	-
Correlation Coefficient		0.177		0.023		

Table 5. Cluster defects at the initial and 12th months examinations

24-2 VF (n, %)		10-2 VF (n, %)		
		Normal	Cluster defect	Total
Initial examination	Normal	21 (37.50%)	4 (7.14%)	25 (44.64%)
	Cluster defect	24 (42.86%)	7 (12.50%)	31 (55.36%)
	Total	45 (80.36%)	11 (19.64%)	56 (100%)
12th months	Normal	26 (46.43%)	3 (5.36%)	29 (51.79%)
	Cluster defect	16 (28.57%)	11 (19.64%)	27 (48.21%)
	Total	42 (75.00%)	14 (25.00%)	56 (100%)

which anatomical and functional deterioration has not yet fully occurred and no significant progression was observed.

As mentioned, none of the studies mentioned above evaluated solely glaucoma suspect cases. Reznicek et al. (22) evaluated the correlation between global indices (MD, PSD) of flicker-defined form perimetry, which is thought to be better at diagnosing preperimetric damage, and peripapillary RNFL in isolated glaucoma suspect cases and they found a significant correlation (r=0.380, p=0.003 for MD and r=–0.516, p<0.001 for PSD). They also divided perimetry into six quadrants (superotemporal, temporal, inferotemporal, inferonasal, nasal, and superonasal) and found that the MS for each quadrant was consistent with the corresponding RNFL thickness. Nevertheless, Nilforushan et al. (23) found the correlation only between inferotemporal RNFL and superonasal VF.

In our study, cluster defects were observed in approximately one-fifth of the patients at the initial examination and in one-fourth of the patients at the 12th month. In addition, 7.14% of the eyes classified as normal according to 24-2 VF at the initial examination had a defect in 10-2 VF. The other way around, the defect in 24-2 VF was observed in 42.85% of the eyes classified as normal according to 10-2 VF. However, De Moraes et al. (16) detected cluster defects in 10-2 VF (46.8%) and 24-2 VF (33.9%) in glaucoma-suspected eyes with a similar frequency. They detected a defect in 10-2 VF in 39.5% of the eyes classified as normal in 24-2 VF. Vice versa, they reported a defect in 24-2 VF in 24.8% of the eyes classified as normal according to 10-2 VF. In another study conducted by Traynis et al. (17) in patients with glaucoma suspects and early glaucoma, cluster defects in 10-2 VF were reported as common as cluster defects in 24-2 VF. While 15.7% of eyes classified as normal in 24-2 VF had cluster defects in 10-2 VF, 20.5% of eyes classified as abnormal in 24-2

VF were found to be normal in 10-2 VF.

When it comes to studies focusing on the central visual field, Na et al. (24) described the area corresponding to the macula in 24-2 VF and evaluated the relationship between the mean sensitivities (MS) of this defined area (in dB and 1/Lambert) and the GCC and macular peripapillary RNFL (mpRNFL). The authors report that there is a statistically significant structure-function relationship (GCC vs MS r=0.111, mpRNFL vs MS r=0.127 for dB) and that the correlation between GCC and VF is stronger than the correlation between mpRNFL and VF in the superior quadrant.

In studies investigating the central visual field via 10-2 VF, Cirafici et al. (25) examined the point-based correlations between 10-2 VF and OCT in primary open-angle glaucoma. A positive correlation was found between GCC thickness and 10-2 VF sensitivities ($r = 0.58$, $p = 0.0012$ and $r = 0.58$, $p = 0.0016$, $r = 0.64$, $p = 0.00049$ in perifovea, superior and inferior hemi-quadrant, respectively). Similarly, Tomairek et al. (26) also found that the defects in 10-2 VF in 7 glaucoma suspect cases with normal 24-2 VF were consistent with the OCT findings (GCC and RNFL). However, in the presented study, no correlation was found between the 10-2 VF mean sensitivities (dB) and either the GCC or RNFL thicknesses at the first or 12th month examination. We also attribute this discrepancy with the literature to the fact that we evaluated glaucoma suspect patients in whom anatomical and functional deterioration had not yet fully developed. Tomairek et al. also examined the glaucoma suspects, but the number of patients was quite small (7 patients).

The main limitations of this study are the small number of patients and short follow-up period. There is a lack of consensus on logarithmic and non-logarithmic assessments of structure-function relationships. Although the non-logarithmic unit (1/Lambert) is more suitable for comparing structural and functional measurements, a significant number of studies reported that logarithmic (dB) scales show stronger clinical correlations and provide more accurate results (20,27,28).

In conclusion, the structure-function relationship is still a controversial issue and continues to be the subject of many studies. Various models have been proposed to examine this relationship but there is no parameter on which consensus has yet been reached. Since Hood et al. showed that macular involvement occurs in approximately 90% of patients with early glaucoma in the first half of the 2010s (29–31), interest in the central visual field has increased. Traynis et al. (17) showed that 16% of eyes with early-stage glaucoma with a normal 24-2 visual field had a deterioration at 10-2. This finding is important in clarifying the structure-function relationship and drawing attention to central involvement in the patient group called "glaucoma suspects" or "pre-perimetric glaucoma" which constitutes the critical group in early diagnosis and treatment. In this study, we aimed to evaluate and explain the structure-function relationship in glaucoma suspect cases in terms of both total (24-2, RNFL) and central visual field (10-2, GCC). However, the fact that the correlation between MD and GCC detected at the first examination did not continue during the follow-ups, the correlation between RNFL and PSD that was not present at the first examination emerged during the follow-ups, the correlation between GCC and 10-2 VF that was detected in various studies but not by us, and the fact that the distribution of cluster defects was reported very differently in various studies indicate that no single parameter explains the structure-function relationship and clinical course with 100% accuracy. This situation emphasizes that in the diagnosis of glaucoma suspects, decision should not be based on a single parameter and a single clinical visit. Actions should be taken according to the multiparametric results obtained in periodic visits.

Disclosures

Ethics Committee Approval: This study was approved by the Ege University Ethics Committee (Date: 22/08/2024, Number: 24-8T/70)

Informed Consent: Written informed consents were obtained from all patients.

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Original Article

Amplitude of Accommodation Measured by Closed-Field Autorefractometer in Children With Bilateral High Hyperopia

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Abstract

Objectives: To assess the amplitude of accommodation by autorefractometer in children with bilateral high hyperopia.

Methods: The records of children with bilateral high hyperopia (+6.00 diopter and above) were investigated. Age, amplitude of accommodation (AA) values and pupil size (PS) changes measured by closed-field autorefractometer (Tonoref III), spherical equivalent (SE), astigmatism, presence of amblyopia, strabismus, and stereopsis were noted. Age-matched emmetropic children were also assessed as control group. Comparisons were statistically performed.

Results: The mean ages of high hyperopia (n=32) and control groups (n=32) were not statistically different (p=0.905). Mean SE values were different in both eyes between groups (p<0.001, p<0.001, right and left eyes, respectively). Mean AA in both eyes were different between groups (p=0.017, p=0.02, right and left eyes, respectively). AA differences between two eyes and pupil size measurements in both eyes (right and left) were not different (p=0.90, p=0.576, p=0.35, respectively). Presence of strabismus and amblyopia were higher in hyperopia group and stereoacuity was better in control group. In hyperopia group, there was statistical difference between patients with and without strabismus regarding to mean AA (p=0.03).

Conclusion: Accommodative amplitude, measured by a closed-field autorefractometer (Tonoref III) was lower in bilateral high hyperopic children. AA difference between two eyes and pupil sizes during accommodation were not different between high hyperopic patients and emmetropic controls. High hyperopic patients with strabismus were found to have better accommodative amplitude.

Keywords: Amplitude of accommodation, high hyperopia, closed-field autorefractometer, strabismus, pupil size

Introduction

Significant hyperopia is stated as hyperopia sufficient to cause symptoms prompting clinical attention. Hyperopia is categorized by the degree of refractive error: Low hyperopia is +2.00D or less, moderate hyperopia ranges from +2.25 to +5.00D, and high hyperopia is +5.25D or more. High hyperopia may cause strabismus and amblyopia (1). Levels greater than 1.00D of hyperopic anisometropia and 5.00D of isometric hyperopia are considered amblyogenic (1). Previous studies reported that children with higher magnitudes of hyperopia tend to demonstrate larger and more variable lags of accommodation, and this may be a danger for abnormal visual development including strabismus and amblyopia (2-4).

As already known, accommodation is the eye's ability to modify the focal length of the lens by changing the curvature

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of the eye lens. Accommodation amplitude (AA) is the accommodation performed to move the focal point from the farthest point to the closest point that can be seen. (5). The objective measurement of accommodation is the refractive changes in the eye measured with an automatic refractor while the subject focuses from a distant target to a near target. Both open- field and closed-field autorefractors might be utilized for measurement of AA and the latter has been widely utilized in ophthalmology clinics (6,7). The NIDEK Tonoref III (NIDEK Co., Ltd., Japan) is a closed-field autorefractor which dynamically and simultaneously measures the AA and also pupil size changes in 30 seconds (7). Previous studies showed a moderate agreement between AA obtained with subjective methods and objective Nidek measurements (7-9). Besides, Weng et al. found good repeatability of objective AA values measured by the Tonoref III. They suggested that measuring AA using the Tonoref III in ophthalmology clinics is feasible (9).

The aim was to investigate the AA of children with bilateral high hyperopia by using a closed-field autorefractor, Tonoref III, and comparison was made between high hyperopic and emmetropic eyes. In addition, the mean AA in high hyperopic children with and without strabismus was investigated.

Methods

This study was conducted at Sakarya University Educational and Research Hospital. Prior approval was taken from the Institutional Review Board (Ethical Committee of Sakarya University, Faculty of Medicine, IRB) (IRB number: E-71522473-050.01.04-285269-277), and informed consent was taken from the parents of each subject. This study was conducted in accordance with the principles of the Helsinki Declaration.

The records of children with bilateral high hyperopia (+6.00 diopter and above, hyperopia group) and children with refractive error between -0.50 and +0.75 (control group) were reviewed. Age and sex of children were noted. The latest ophthalmological examination results including best corrected visual acuity (BCVA), eye movements, presence and type of strabismus if present and stereopsis were noted. The age to start using glasses and duration of follow-up were also noted. All bilateral high hyperopic children underwent optical correction considering the presence of strabismus, amblyopia, and dynamic retinoscopy findings. Amblyopia status was also noted. Recovery from amblyopia is defined as interocular difference of one line or none in visual acuity tables.

Amplitude of accommodation (AA) values and pupil size (PS) changes were measured by closed-field autorefractometer (Tonoref III) in each eye, before cycloplegic refraction examination. The difference between AA of each eye were also noted to assess asymmetrical accommodation. In order to keep the pupil steady, the room lighting was dimmed at the headrest of the device on which the patient was seated. All measurements were taken under the same conditions and at the same time of the day (10:00-12:00 AM). Ten minutes were left between right and left eye measurements to avoid the effect of fatigue.

The autorefractor function measures AA by focusing on a target approaching from a far distance. AA between 0-10 D, and pupil diameter between 3 to 8.5 mm can be measured by the device.

Cycloplegic refraction was performed to all patients. Cyclopentolate Hydrochloride 1% topical agent is applied as one drop and repeated after 5 minutes. Cycloplegia action occurs in 30 to 45 minutes of instillation. After 45-60 minutes, refraction was calculated by autorefractometer or handheld retinoscopy. Spherical equivalent (SE) and degree of astigmatisma were noted. The AA, SE, astigmatism, pupil size diameter measurements were extracted from the latest ophthalmic visit.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 20.0 (Statistical Package for Scientific Studies for Windows, SPSS Inc., Chicago, IL) was used for analysis. Comparisons were statistically performed between groups. Normality for distribution of variables was determined by the Kolmogorov-Smirnov test. Student-t-test was used to compare the mean values of two given samples and chi-square test was used to compare categorical variables. The correlation coefficient and significance between mean SE and AA in both eyes were determined using the Pearson Correlation test. A p-value of <0.05 was considered statistically significant.

Results

The records of 32 (64 eyes) patients and age-matched 32 (64 eyes) control subjects were evaluated. Presence of unilateral amblyopia (n: 9) was higher in hyperopia group and stereoacuity was better in control group. Of these 9 amblyopic patients, 4 recovered from amblyopia, 5 did not (12.5%). The mean age to start using glasses was 3.9±1.5 years and the duration of follow-up was 66.3±26.16 months. Table 1 reveals characteristics of two groups. In the hyperopia group, 14 patients had no strabismus and 18 had horizontal strabismus. The mean AAs of hyperopic patients with and without strabismus were 3.8±1.57 and 2.84±1.81 diopter, respectively (p:0.03).

Significant differences were found in terms of mean SE, astigmatism values, mean AA in right and left eyes. The AA difference between two eyes were not different between groups. Pupil size measurements in both eyes were not different between groups. Table 2 reveals refractive parameters of both groups and p-values.

Table 1. The characteristics of Hyperopia and Control Groups

	Hyperopia Group	Control Group	p
The mean age (years)	9.37±2.09	9.44±2.08	p=0.90
Presence of stereopsis (%)	53.1	100	p<0.001
Presence of amblyopia (%)	28.1	0	p<0.001
Presence of strabismus (%)	56.2	3.1	p<0.001

Table 2. The refractive parameters of eyes in Hyperopia and Control Groups

	Hyperopia Group	Control Group	p
Mean AA OD (diopter)	3.28±1.59	4.37±1.91	p=0.017
Mean AA OS (diopter)	3.57±1.88	4.83±2.32	p=0.02
AA difference (diopter)	1.43±1.06	1.39±1.08	p=0.90
Mean Pupil size OD	6.54±0.64	6.64±0.85	p=0.57
Mean Pupil size OS	6.55±0.75	6.73±0.8	p=0.35
Mean SE OD (diopter)	7.15±1.08	-0.14±0.4	p<0.001
Mean SE OS (diopter)	6.99±1.10	-0.78±0.38	p<0.001
Mean astigmatism OD	0.96±0.45	-0.17±0.28	p<0.001
Mean astigmatism OS	0.94±0.44	-0.16±0.3	p<0.001

AA: Amplitude of accommodation OD: Oculus dexter OS: Oculus sinister

Discussion

In this study, strabismus was found to be more common in bilateral high hyperopic children compared to emmetropes and mean AA was lower in hyperopia group. Besides, the mean AA was found to be statistically higher in hyperopic children with strabismus compared to hyperopic children without strabismus. Ingram et al. found that individuals who developed strabismus had larger accommodative deficits (10). Author also suggested that the infants who neither accommodate nor emmetropize have a defect in blur sensitivity and that these are risk factors for strabismus and amblyopia development (10). Studies revealed that patients who have accommodation deficits might be at risk for poor emmetropization, strabismus, and amblyopia (11). In our study, horizontal strabismus in bilateral hyperopic patients, regardless of eso- or exotropia, was more frequent in those with higher amplitude of accommodation. Variable accommodative effort may be the cause of eye squint in bilateral high hyperopic children or the small sample size may alter the statistical results.

Amblyopia was seen more common in these bilateral hyperopic patients than healthy controls. On the other hand, amblyopia was not as common as strabismus in bilateral hyperopic patients. Only 12.5% of bilateral hyperopic patient had persistent unilateral amblyopia. We have already known that isoametropic amblyopia may occur in the presence of 4.0–5.0 D or more of hyperopia but we did not see bilateral amblyopia in our cohort (12). Ziylan et al. found that 16.1% of high hyperopic children had isoametropic amblyopia (13). Atkinson et al. observed that correction of hyperopia in high hyperopic infants caused a decline in the incidence of strabismus and poor acuity at 3.5 years of age compared to uncorrected patient group with comparable refractive errors. In line of this report, the mean age to start using glasses were low, in our study. Early screening and correction is very important in bilateral high hyperopic patients (14).

Candy et. al. suggested that the risk of failure to emmetropize rises most dramatically above 4 D of hyperopia in nonamblyopic and nonstrabismic individuals (3). Horwood et al. found that accommodation for near was better in hypermetropic ones who go on to emmetropize (15). Hornoch et al. reported that most 5- to 24-month-olds accommodated well with moderate hyperopia, but high hyperopia above 4.0 D is associated with abnormal accommodative performance. Larger accommodation lags were linked with higher spherical equivalent refractive error, although only with hyperopia ≥4.0 D - ≥1.25 D lags were seen in a majority of children (16). In our cohort, based on autorefractometer measurements, amplitude of accommodation was also low in high hyperopic patients compared to healthy controls but the mean pupil size during accommodation was not different among groups. In the light of these data, it was suggested that high hyperopia is associated with low accommodative amplitude and near reflex impairment independent of focal depth. In clinical practice, low AA should be kept in mind when prescribing glasses for these children, and the prescription should be determined by performing examinations for accommodation.

Asymmetrical accommodation was found to be common in anisometropic amblyopes, previously (17). In our study, the difference in AA between the two eyes was not different between high hyperopic and emmetropic children is probably due to the fact that high hyperopia is bilateral.

The major limitation of the study was the small sample size. Because of this, the statistical analysis may have been un-

derpowered. On the other hand, this study is the first which evaluates amplitude of accommodation by using closed-field autorefractometer in bilateral high hyperopic children. In future studies, grouping hyperopia into low, moderate, and high categories and comparing them can also provide us with useful information.

Conclusion

The mean AA was low in bilateral high hyperopic children. Besides, the mean AA was higher in hyperopic children with strabismus than in hyperopic children without strabismus. The mean AA difference between two eyes and pupil sizes during accommodation were not different between emmetropic and high hyperopic children.

Disclosures

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Original Article

Refractive Error Changes at Near After Smartphone Use

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Abstract

Objectives: To quantify short-timescale refractive recovery after a standardized smartphone near task and timed distance-viewing breaks aligned with the 20-20-20 paradigm, and to determine how much of the accommodative/near work-induced transient myopia (NITM) recovery occurs within the earliest seconds of a break.

Methods: In this cross-sectional, 58 students symptomatic for digital eye strain (Computer Vision Syndrome Questionnaire score ≥ 6) completed a 20-minute continuous reading task on smartphone. Objective refractive error was recorded with an open-field autorefractor at baseline, immediately post-task, and after distance-viewing breaks of 20 seconds, 1 minute, and 2 minutes (≥6 m fixation; no near work permitted).

Results: The mean age of participants was 20.85±1.43 years. At baseline near fixation, mean sphere and SE were −2.08±0.45 and−2.38±0.46 D, respectively. Immediately after 20 minutes of reading, a myopic shift was evident (sphere −2.12±0.50 D; SE −2.47±0.46 D). During distance breaks, refractive measures recovered toward baseline in a biphasic pattern: A significant early recovery within 20 seconds (sphere P=0.007; SE P=0.005), followed by smaller improvements from 20 to 60 seconds (sphere P=0.266; SE P=0.034) and from 60 to 120 seconds (sphere P=0.415; SE P=0.270). Cylinder remained stable across conditions (≈ −0.6 D; P=0.136), whereas sphere and SE varied significantly across near and break intervals (both P<0.001).

Conclusion: After a 20-minute smartphone near task, the largest component of refractive recovery occurs within the first 20 seconds of distance fixation, with diminishing returns up to 2 minutes. This objective kinetics support the refocusing premise of the 20-20-20 approach and indicate that incorporating more frequent distance-viewing breaks can capture most accommodative/NITM recovery (20–2 min–20).

Keywords: Accommodation, digital eye strain, near work-induced transient myopia, open-field autorefractor, 20-20-20 rule

Introduction

Digital eye strain (DES), historically termed computer vision syndrome (CVS), includes internal symptoms (eyestrain, ache, headache, blur) and external symptoms (burning, irritation, tearing, dryness, photophobia) that are precipitated or exacerbated by sustained near work, particularly on electronic displays (1,2). With widespread smartphone use in student populations, DES has become a prevalent and clinically important issue (3-5). Symptom burden can be assessed using validated instruments such as the Computer Vision Syndrome Questionnaire (CVS-Q), including Persian adaptations that support standardized evaluation across settings (6-8). Physiologically, prolonged near viewing disrupts accommodation and vergence, leading to accommodative

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lag during the task and a transient post-task myopic aftereffect—near work–induced transient myopia (NITM)—which contributes to visual discomfort and blur on distance fixation (1,9-13).

NITM is commonly reported in the range of approximately 0.12–0.60 D, with recovery toward baseline typically occurring over about 20–70 seconds under closed-loop viewing; however, both magnitude and decay depend on task features and refractive status (11-13). Myopic individuals often demonstrate larger initial NITM and slower decay compared with emmetropes (11-13). These accommodative/refractive dynamics can be quantified objectively using open-field autorefractors (14,15), and prior work indicates good short-term reproducibility for initial NITM and its early decay phase (16). Beyond NITM, short periods of smartphone use (≈20–30 minutes) have been associated with increased accommodative lag, reduced accommodative amplitude and facility, and deterioration in convergence measures such as near point of convergence and fusional vergences, particularly in adolescents and young adults (5,17,18). Together with decreased blink rate and tear-film instability during screen use, these mechanisms are thought to underlie the symptom profile observed in DES (1,3).

To mitigate visual fatigue, frequent brief distance-viewing breaks are widely recommended. The 20-20-20 rule—every 20 minutes, look 20 feet away for 20 seconds—originated from practical visual ergonomics emphasizing regular breaks (19). Evidence for its effectiveness is mixed. A software-assisted, real-world reminder intervention implementing the 20-20-20 schedule increased break frequency, reduced continuous device use, and improved DES/dry-eye symptoms and binocular accommodative facility, although ocular surface signs did not consistently change and benefits were not always sustained after discontinuation (20). In contrast, a controlled laboratory study that inserted 20-second breaks at varying intervals (every 5, 10, 20, or 40 minutes) during a single 40-minute demanding task found no significant differences in DES symptoms between schedules (21). Given that refractive state change is central to shifting fixation between near and distance, characterizing objective refractive recovery during brief breaks may help clarify how much break time is needed for near refraction to return toward baseline.

Importantly, multiple studies describe a robust biphasic recovery pattern: the largest component of accommodative/NITM decay occurs rapidly within the first 20–60 seconds of distance fixation, followed by smaller and slower gains thereafter (11-13,22), suggesting that even a 20-second distance fixation may capture a substantial proportion of recovery. However, few investigations have directly linked real-world smartphone reading to moment-by-moment refractive recovery during short, timed breaks aligned with the 20-20-20 framework.

Accordingly, the present study used a 20-minute smartphone near task followed by 20-, 60-, and 120-second distance-viewing breaks to quantify objective refractive recovery and determine how much recovery occurs in the earliest seconds of a break (19,20).

Methods

This analytical cross-sectional study used a within-participant repeated-measures design to quantify changes in refractive state at five time points surrounding a 20-20-20 style break paradigm. Students from Shahid Beheshti University of Medical Sciences were screened with the validated Persian version of the CVS-Q (7). Individuals with a CVS-Q score of 6 or higher who reported at least three hours per day of digital device use over the prior month were invited to participate using convenience sampling.

Exclusion criteria were history of refractive surgery; contact lens wear within the preceding month; clinically evident ocular surface disease including dry eye, blepharitis, or meibomian gland dysfunction; Sjögren syndrome; systemic disease known to affect refraction such as diabetes; medications affecting the tear film (for example antihistamines or antidepressants); amblyopia or strabismus; and receipt of common CVS treatments within the prior month. The study protocol received approval from the Ethical Committee of Shahid Beheshti University of Medical Sciences (Approval ID: IR.SBMU.RETECH.REC.1403.029, Date: 28/04/2024). All procedures were performed in compliance with the principles of the Helsinki Declaration, and written informed consent was obtained from all participants.

The primary outcome was the objective refractive state (sphere, cylinder, and spherical equivalent) measured in diopters with an open-field autorefractor (Nippon-Shin k-5001 Nvision, Japan). Measurements were performed with best correction in place when required to achieve optimal acuity.

Testing was carried out in a controlled environment with constant room lighting at typical clinical mesopic–photopic levels. Participants were asked to refrain from any near work for at least 10 minutes before baseline measurements. The open-field configuration permitted natural fixation at a distance target during baseline and recovery measurements.

The experimental sequence comprised five time points in a fixed order: before reading distance (baseline), and near (baseline), immediately after 20 minutes of continuous reading, and then after 20 seconds, 1 minute, and 2 minutes of distance-viewing breaks. For the near task, participants read continuously on their personal smartphone for 20 minutes at their habitual working distance, which was typically around 30- 40 cm and was not constrained to avoid altering normal behavior. Immediately upon completing the 20-minute reading period, participants were positioned at the autorefractor

for measurement. During each break interval, participants were instructed to maintain relaxed distance fixation (≥6 m equivalent), avoid any near fixation or phone use, and then return immediately to the autorefractor for the subsequent measurement at near at 20 seconds, 1 minute, and 2 minutes, respectively. At each time point, three consecutive readings per eye were obtained and averaged. The autorefractor outputs were recorded in negative cylinder notation, and SE was computed as sphere plus one-half cylinder.

Both eyes were measured at all time points. For the analysis, only the right-eye refractive state was analyzed at each time point, with sphere, cylinder, and SE computed from three consecutive readings and averaged.

Descriptive statistics included the mean, standard deviation, and range for sphere, cylinder, and SE at each of the five time points. All statistical analyses were performed in SPSS (version 26) (SPSS Inc., Chicago, Illinois, USA). Distributional assumptions were examined using Shapiro–Wilk tests, which indicated that all variables at all time points deviated from normality. Accordingly, changes across time were evaluated with the nonparametric Friedman test, and pairwise comparisons were conducted using Wilcoxon signed-rank tests with Bonferroni adjustment for multiple testing. The primary comparison was the change in SE across the five conditions, with sphere and cylinder treated as secondary outcomes. A two-sided alpha of 0.05 was adopted for significance, with multiplicity adjustments applied as described. Graphical presentations were created in MedCalc Statistical Software version 20.218 (MedCalc Software Ltd, Ostend, Belgium). Astigmatic vector analysis was performed using AstigMATIC software (23).

Results

Fifty-three participants were included (mean age 20.85±1.43 years; range 18–23). The sample comprised 13 men (24.5%) and 40 women (75.5%). The mean CVS-Q score was 11.72±5.18 (range 6–29), confirming symptomatic CVS in all enrolled participants.

Descriptive outcomes

As shown in Table 1, at baseline distance fixation, the right eye showed a mean sphere of −0.18±0.82 D and a mean SE of −0.42±0.85 D. During near viewing, refractive measures shifted in the myopic direction relative to baseline distance: near-baseline sphere was −2.08±0.45 D and SE was −2.38±0.46 D, and immediately after 20 minutes of continuous reading these values were −2.12±0.50 D (sphere) and −2.47±0.46 D (SE). During distance-viewing breaks, a gradual recovery toward less myopic values was observed: at 20 seconds, sphere was −2.01±0.51 D and SE was −2.35±0.51 D; at 1 minute, sphere was −1.98±0.42 D and SE was −2.28±0.46 D; and at 2 minutes, sphere was −1.91±0.57 D and SE was −2.21±0.51 D (Fig. 1, 2). Cylinder remained relatively stable across conditions (approximately −0.60 D on average), and its overall change did not reach statistical significance (Friedman P=0.136) (Fig. 3). In contrast, SE showed highly significant changes across near-task and recovery time points (Friedman P<0.001), and sphere followed a similar pattern (Friedman P<0.001).

Pairwise comparisons and recovery pattern

Wilcoxon signed-rank tests indicated no significant change between near-baseline and immediately after 20 minutes of near work for sphere (Z=−1.612, P=0.107) and significant for SE (Z=−1.993, P=0.046). A significant recovery toward less myopic values occurred within the first 20 seconds for both sphere (Z=−2.690, P=0.007) and SE (Z=−2.790, P=0.005). Subsequent intervals showed smaller, non-significant stepwise changes from 20 to 60 seconds for sphere (Z=−1.112, P=0.266) and SE (Z=−2.116, P=0.034), and from 60 to 120 seconds for sphere (Z=−0.814, P=0.415) and SE (Z=−1.103, P=0.270). The largest and statistically robust component of accommodative/refractive recovery occurs within the first 20 seconds, with more modest, statistically non-significant improvements thereafter up to 2 minutes.

Table 1. Right-eye refractive measures at distance and across near-task and break intervals: mean±SD (range)

	Baseline Far	Near					p*
		Baseline Near	After 20 min reading	Break			
				20 second	1 minute	2 minutes	
Sphere (D)	−0.18±0.82 (−2.25 to +1.37)	−2.08±0.45 (−3.37 to −1.12)	−2.12±0.50 (−3.50 to −0.25)	−2.01±0.51 (−3.50 to −0.50)	−1.98±0.42 (−3.25 to −1.00)	−1.91±0.57 (−3.50 to −0.37)	<0.001
Cylinder (D)	−0.50±0.34 (−1.25 to 0.00)	−0.60±0.36 (−1.75 to 0.00)	−0.69±0.56 (−3.50 to 0.00)	−0.66±0.39 (−1.62 to 0.00)	−0.60±0.47 (−2.62 to 0.00)	−0.60±0.45 (−2.50 to 0.00)	0.136
SE (D)	−0.42±0.85 (−2.62 to +1.00)	−2.38±0.46 (−3.93 to −1.75)	−2.47±0.46 (−4.06 to −1.31)	−2.35±0.51 (−4.06 to −1.06)	−2.28±0.46 (−3.94 to −1.31)	−2.21±0.51 (−4.06 to −1.25)	<0.001

* Friedman Test (for near), D, diopter; SE, spherical equivalent

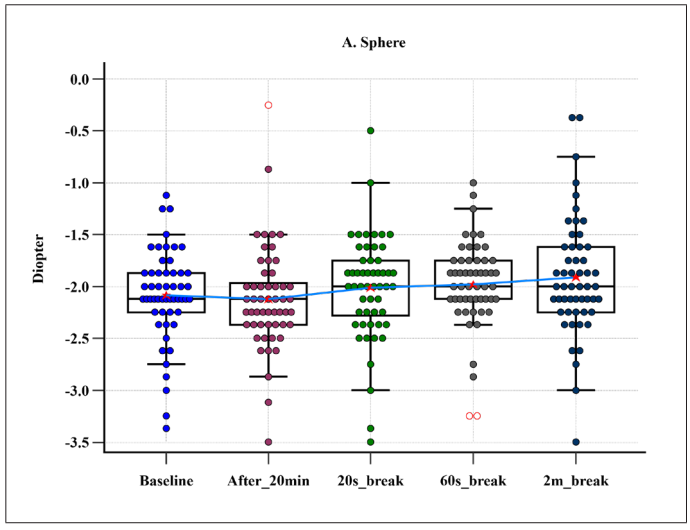

Figure 1. Near-task recovery curves for right-eye spherical refractive error component following 20 minutes of reading.

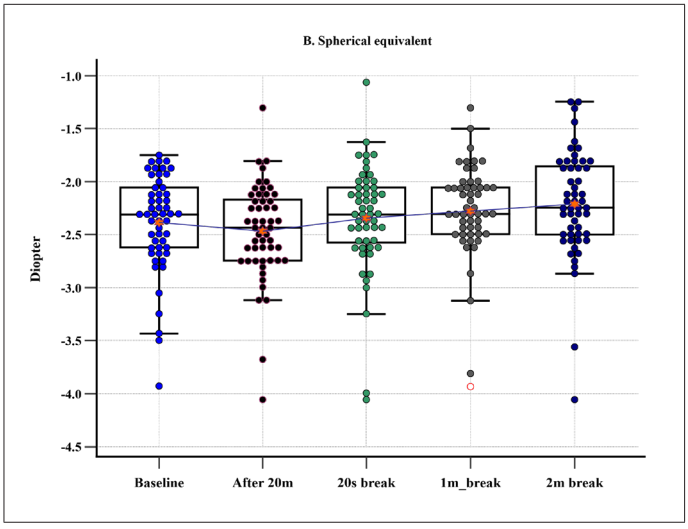

Figure 2. Near-task recovery curves for right-eye spherical equivalent following 20 minutes of reading.

Discussion

This study quantified the shorttimescale recovery of objective refractive state following 20 minutes of continuous smartphone reading and a sequence of distanceviewing breaks aligned with the 202020 paradigm. Three principal findings emerged. First, immediately after near work there was only a mild change in near SE relative to near baseline SE, Second, the largest, statistically robust component of recovery toward baseline occurred within the first 20 seconds of distance fixation, with diminishing, often nonsignificant improvements from 20 to 60 and 60 to 120 seconds. Third, cylinder remained relatively stable across conditions, whereas sphere and SE varied significantly across near and break intervals.

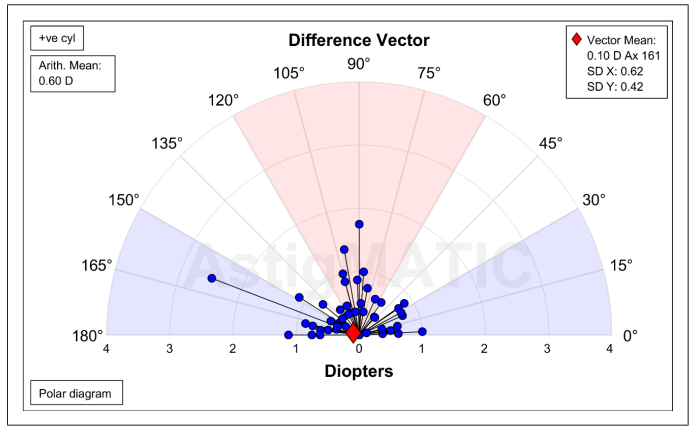

Figure 3. Difference-vector polar diagram showing changes in astigmatism between "after 20 minutes of reading" and "after a 2minute break." Each blue dot represents an individual eye's difference vector; the red diamond denotes the mean vector. Distances from the origin indicate the magnitude of astigmatic change in diopters, and angles indicate axis change.

These observations align closely with the classic NITM literature, which shows initial posttask myopic shifts typically on the order of 0.12–0.60 D and a biphasic decay that returns toward pretask baseline largely within tens of seconds under closedloop viewing (11-13). Ciuffreda and colleagues described larger initial NITM and slower decay in myopes relative to emmetropes (11,12), and several studies have reproduced the rapid early phase and slower late phase of decay that we observed (13,22). Although our cohort was not stratified by refractive status, the time course we report is consistent with these prior patterns and supports the generalizability of the biphasic recovery across tasks and platforms. Importantly, our measurements were obtained with an openfield autorefractor, a modality shown to be reliable for both static and dynamic accommodation/NITM assessments (14-16). WinHall et al. demonstrated that WAM5500 static and dynamic recordings yield comparable stimulusresponse functions at lower demands and predictable differences at higher demands, with acceptable limits of agreement (14). Moreover, Lin et al. showed excellent repeatability for the initial NITM and its early decay (first ~50 s), with ICCs ≥0.90, reinforcing the robustness of the time window emphasized by our protocol (16).

Study finding that the greatest refractive recovery occurred within 20 seconds of distance fixation has practical implications for the 202020 rule. While clinical and field evidence for symptom reduction with 20second breaks has been mixed (20,21), the physiological premise that a brief distance fixation captures a substantial fraction of accommodative/NITM recovery is supported by our data and prior laboratory work (11-13,22). TalensEstarelles et al. reported that softwareprompted 20second breaks every 20 minutes

reduced DES and dry eye symptoms and increased binocular accommodative facility in symptomatic users, although changes in ocular surface signs were limited and some effects were not sustained after discontinuation (20). Conversely, Johnson and Rosenfield (21) found no symptom benefit when 20second breaks were inserted at varying intervals (5–40 minutes) during a single cognitively demanding task. The results of present study help reconcile these findings by focusing on recovery kinetics: even if subjective symptoms do not always improve with short prompts in a single sitting, the objective accommodative/ refractive system recovers rapidly in the earliest seconds of distance fixation. Thus, a 20second break appears to be physiologically meaningful for refocusing, though the translation to symptom relief likely depends on additional factors (task demands, individual susceptibility, tear film, and total break dose across the day) (20,21).

The stability of cylinder across conditions further indicates that the primary refractive dynamics during and after near work are driven by spherical/SE components tied to accommodation rather than by systematic changes in astigmatism. This agrees with prior NITM work in which the principal posttask refractive change is a myopic shift in SE, with astigmatic components showing little systematic modulation (11-13). Our differencevector polar analysis between "after 20 minutes" and "after a 2minute break" corroborated the small net mean astigmatic change, despite some interindividual variability in axis/magnitude.

With respect to the device/task domain, recent work indicates that smartphone near tasks of 20–30 minutes can degrade accommodative and vergence function acutely (decreased amplitude/facility, increased lag; reduced NPC/reserves) (5,17,18), while controlled comparisons show broadly similar accommodative consequences between mobile phone and printed text at typical reading distances (15). The protocol—20 minutes on a personal smartphone at habitual working distance—maps onto these durations and distances, and the recovery data are consistent with reports that the immediate refixation to distance after near work elicits a transient myopic shift followed by a rapid decay in the first tens of seconds (11-13,15,22). The present refractive time course also dovetails with Redondo et al., who found that more frequent or selfpaced breaks (every 10 minutes or individualized) reduced certain DES symptoms, stabilized accommodative variability, and minimized initial NITM compared with no break or a single 20minute break condition (the latter paralleling the 202020 cadence) (21). Although their focus was a 40minute desktop task and their outcomes included variability and symptoms, both studies converge on the idea that early and/or more frequent breaks confer physiological benefit relative to uninterrupted near work.

Methodological considerations include the withinparticipant design, controlled lighting, and openfield measurements that allow natural fixation, which strengthen internal validity. The authors limited analyses to righteye refractive state for consistency; however, both eyes were measured at all time points. The present study did not stratify by refractive error or quantify tearfilm parameters; prior studies suggest that refractive status can modulate NITM magnitude/decay (11, 12, 22), and ocular surface factors may affect symptom responses to breaks (20,21). Our sample comprised symptomatic students (CVSQ≥6), aligning with prior DES breakrule investigations (20) and increasing clinical relevance, but potentially limiting generalizability to asymptomatic populations (21). Finally, while our 20second, 1minute, and 2minute breaks characterize shortinterval recovery, longer observation windows can reveal slower latephase dynamics (11-13,16,22).

A key limitation of this study is the absence of cycloplegic refraction. Because our objective was to quantify short-timescale, accommodation-related refractive changes (near work–induced transient myopia) and their recovery during brief distance-viewing breaks, measurements were intentionally obtained under non-cycloplegic conditions using an open-field autorefractor. Therefore, the results should be interpreted as reflecting dynamic, non-cycloplegic refractive recovery kinetics rather than "true" cycloplegic refractive error, and caution is warranted when extrapolating these findings to cycloplegic conditions.

A key translational contribution of this study is reframing traditional break guidance. While the popular 202020 rule is widely promoted, evidence for symptom relief has been mixed. Clinically, these findings support recommending brief, regular distanceviewing breaks during sustained smartphone use. A 20second break likely captures most of the early accommodative benefit, with only slight additional gains beyond about 1 minute.

Disclosures

Ethics Committee Approval: The study protocol received approval from the Ethical Committee of Shahid Beheshti University of Medical Sciences (No: IR.SBMU.RETECH.REC.1403.029, Date: 28/04/2024)

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Original Article

Automatic Diagnosis of Plus Disease in Retinopathy of Prematurity Using Deep Learning

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Abstract

Objectives: Plus disease, which can be diagnosed during clinical ophthalmoscopic examinations, is the most important feature in determining retinopathy of prematurity (ROP) requiring treatment. In the current study, we aimed to automatic diagnose and predict plus disease based on deep learning (DL) from retinal images of infants with ROP.

Methods: 600 retinal images from infants screened for ROP were evaluated. Each image was classified as normal, pre-plus and plus disease. After image pre-processing, the images were distributed into groups equal to the number of normal eye images and were used for training DL algorithms such as EfficientNetB7, InceptionResNetV2 and VGG16. The algorithms were trained with 10-fold cross-validation, and results are reported as sensitivity, specificity, accuracy, receiver operating characteristic (ROC) curve, and area under the curve (AUC).

Results: Of the 600 retinal images included, 258 images obtained after pre-processing were graded as 86 (33.3%) normal, 86 (33.3%) as pre-plus disease, and 86 (33.3%) as plus disease. For plus versus no-plus disease diagnosis, among the algorithms, InceptionResNetV2 achieved 0.90 sensitivity, 0.92 specificity, and 0.91 accuracy. Area under the ROC curve was 0.91. For detection of pre-plus disease or worse versus normal, the algorithm achieved 0.81 sensitivity, 0.97 specificity, and 0.88 accuracy.

Conclusion: Our results showed that DL algorithms can automatically diagnose plus disease in ROP with high sensitivity, high specificity, and high accuracy.

Keywords: Deep learning, fundus images, plus disease, retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP), a disease of the developing retina characterized by abnormal retinal vascular development in premature infants, is the leading cause of childhood blindness worldwide (1,2). The clinical diagnosis of ROP is standardized by the International Classification of ROP (ICROP), which was developed in the 1980s and revised in 2005 and 2021 (3-5). While most cases regress spontaneously without requiring treatment, 5% to 10% may progress to severe ROP with fibrovascular proliferation and retinal detachment leading to permanent blindness (1,2). The hallmark of severe ROP requiring treatment is plus disease, defined as arterial tortuosity and venous dilatation of the posterior retinal blood vessels equal to or greater than standard retinal photographs selected and published according to expert consensus (1,6). However, in the 2005 revised ICROP, retinal vascular abnormalities with greater than normal but insufficient for plus disease were defined

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as pre-plus disease (4). In ICROP in 2021, it was emphasized that pre-plus and plus disease represent a continuous spectrum of retinal vascular changes (5). Studies have shown that severe ROP accompanied by plus disease can be treated with laser photocoagulation (LP) or intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, while infants diagnosed with pre-plus require close observation (1,2,7). Therefore, timely and accurate diagnosis of plus disease is important.

Deep learning (DL) algorithms, which are increasingly used today, have gained importance as an artificial intelligence (AI) algorithm that has the potential for disease classification through automatic image analysis (8). In recent years, the number of studies showing that DL approaches, as well as ROP experts, can detect or classify ROP has been increasing. On the other hand, research has revealed that there may be differences between experts in the diagnosis of plus disease (9-13). Therefore, in the current study, we aimed to automatic diagnose and predict plus disease based on DL from retinal images of infants with ROP.

Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki, following the approval of the Ethical Review Committee (No: 2024/05, Date: 23/05/2024). Written informed consent was obtained from the parents of all infants participating in the study.

Datasets

Six-hundred retinal images obtained during routine ROP examinations between January 2017 and December 2023 were evaluated for this study. These images were taken from each premature infant who met national screening guideline (14) (gestational age (GA) of less than 34 weeks and birth weight (BW) of 1700 g or less or GA of 34 weeks or greater and BW greater than 1700 g, whose clinical condition was unstable) using a commercially-available camera (Heine Video Omega® 2C indirect ophthalmoscope; Heine Optotechnik, Herrsching, Germany). All images containing a view of the posterior pole, including the optic disc and vascular arcades were independently graded by two experienced ROP experts based on ICROP criteria as normal, pre-plus, or plus disease. Additionally, inter-grader agreement was assessed using the weighted Cohen's kappa coefficient (κ=0.75), which indicates substantial agreement, to account for the ordinal nature of disease severity. Grading was performed independently, and discrepancies were resolved by consensus. Although they were taken during the examination, images taken from the peripheral retina were not evaluated.

Image selection and pre-processing

Of the 600 retinal images initially collected, only 258 were included in the final analysis after applying image quality and eligibility criteria. Images with poor quality due to factors such as focusing problems, contrast deficiencies, motion blur or insufficient illumination or those that did not adequately visualize the posterior pole, including the optic disc and vascular arches, were excluded. Therefore, before training the algorithm, pre-processing steps were applied. By determining the lens area in the raw images, parts containing noise and no meaningful data were eliminated using the Edge Attention and Adaptive Background Removal algorithm (15). Blurring from the images was eliminated using Contrast Limited Adaptive Histogram Equalization (CLAHE) (16). Finally, the images were resized (224x224x3) to make them suitable for training the algorithm. After the images were pre-processed, the images were distributed into groups as normal, pre-plus disease and plus disease, equal to the number of normal eye images and were used for training DL algorithms.

DL Algorithm Development and Performance Evaluation

Three types of DL algorithms were used to train the images after pre-processing: EfficientNetB7, InceptionResNetV2 and VGG16. These algorithms, based on the convolutional neural networks (CNN) principle, are architectures that offer different approaches to the production of new data and have various advantages such as high performance, efficiency and scalability features (17-19). A 10-fold cross-validation (CV) procedure was performed to evaluate the performance of the algorithms, where the dataset was divided into 10 folds; in each iteration, 9 folds (90%, n=232) were used for training and 1 fold (10%, n=26) was used for testing. More importantly, to prevent data leakage, images of the same infant were not distributed across different folds. Instead, all samples of a specific infant were assigned to a single fold. Therefore, no image of the same infant was simultaneously present in both the training and test sets. In this way, the risk of memorizing the algorithm is reduced and the model performance is allowed to be evaluated independently of the subsets. Additionally, the performances of the algorithms under equal conditions were compared using 50 epochs and 0.001 learning rate parameters in all experiments.

The performance of the algorithms was reported as sensitivity, specificity, accuracy, receiver operating characteristic (ROC) curve, and area under the curve (AUC). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 25.0. A *P* value of less than 0.05 was considered statistically significant.

Results

Of the 300 infants reviewed for this study, 86 (28.6%) were diagnosed with plus disease. Laser photocoagulation and/or intravitreal bevacizumab injection treatment was applied to 167 eyes of 86 infants diagnosed with plus disease. Seventy-one (12.3%) eyes received laser photocoagulation, 58 (10%) eyes received intravitreal bevacizumab and 38 (6.3%) eyes received laser photocoagulation and intravitreal bevacizumab together. The mean GA (27 ± 2 weeks) and mean BW (1013 ± 312 g) of these infants requiring treatment were significantly lower than infants diagnosed with pre-plus disease (29.7 ± 2 weeks, 1438 ± 480 g) and normal (29.9 ± 1.6 weeks, 1490 ± 356 g) (p=0.000 for GA and BW). Infants diagnosed with pre-plus disease were followed closely and it was observed that ROP spontaneously regressed without the need for any treatment.

600 retinal images of 300 infants were reviewed for eligibility in this study. Of these, 258 images obtained after pre-processing were graded as 86 (33.3%) normal, 86 (33.3%) as pre-plus disease, and 86 (33.3%) as plus disease, equal to the number of normal eye images (n=86). The results of three types of DL algorithms for the diagnosis of plus disease were analyzed. As shown in Table 1, for plus versus no-plus disease diagnosis, among the algorithms, InceptionResNetV2 achieved 0.90 sensitivity, 0.92 specificity, and 0.91 accuracy. Area under the ROC curve was 0.91. For detection of pre-plus disease or worse versus normal, the algorithm achieved 0.81 sensitivity, 0.97 specificity, and 0.88 accuracy. When compared with InceptionResNetV2 for the diagnosis of plus versus no-plus disease, we observed that

Table 1. Performance of each algorithm

	Accuracy	Sensitivity	Specificity	AUC
EfficientNetB7				
plus vs. no-plus	0.85	0.82	0.88	0.85
pre-plus or worse vs. normal	0.91	0.83	0.96	N/A
InceptionResNetV2				
plus vs. no-plus	0.91	0.90	0.92	0.91
pre-plus or worse vs. normal	0.88	0.81	0.97	N/A
GVV16				
plus vs. no-plus	0.91	0.97	0.87	0.90
pre-plus or worse vs. normal	0.90	0.83	0.99	N/A

AUC: Area under curve; N/A: Not applicable

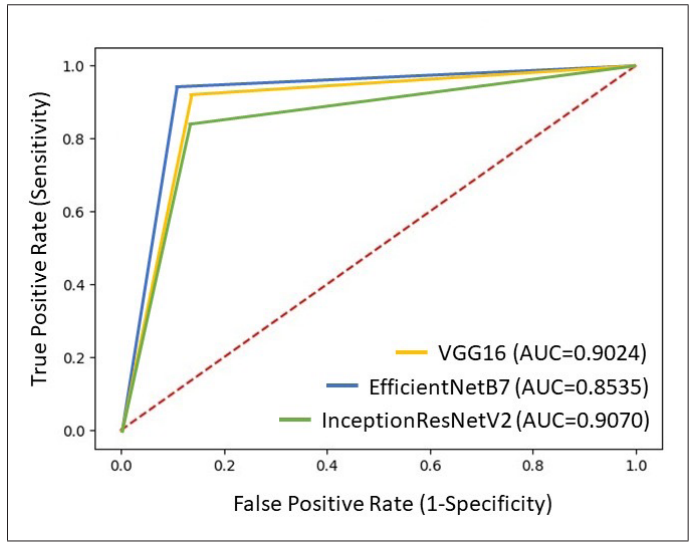

Figure 1. A receiver operating characteristic (ROC) curve and area under the curve (AUC) values of of three DL algorithms for predicting plus disease images (vs. no-plus disease).

EfficientNetB7 and VGG16 could predict plus disease at similar rates, while VGG16 achieved the highest sensitivity value (0.97 sensitivity). Again, for the diagnosis of pre-plus disease or worse versus normal, we found that all 3 algorithms exhibited close prediction rates and could predict with high specificity (0.96, 0.97, 0.99 for EfficientNetB7, InceptionResNetV2 and VGG16, respectively). The performance of each algorithm is shown in Table 1. ROC curves of three DL algorithms for predicting plus disease images (vs. no-plus disease) are shown in Figure 1.

Discussion

This study presents the performance of DL algorithms trained using retinal images in diagnosing and predicting plus disease. Key findings include: 1. Plus disease can be diagnosed with high sensitivity, high specificity and high accuracy with the DL algorithms used. 2. in addition to detecting plus disease, the trained algorithms can also guide the detection of pre-plus disease. 3. it can be used to support clinical diagnosis in the future because of its ability to detect normals vs pre-plus or worse.

In 2007, Chiang et al. analyzed the consensus in plus disease diagnosis. In this study, where a dataset of 34 retinal images was interpreted by 22 ROP experts, the results indicated that the consensus rate was low both in the plus-no-plus distinction (21%) and in the plus-pre-plus and neither (12%) distinctions (20). Another study examined the diagnostic process of experts using qualitative research techniques in the diagnosis of plus disease in ROP and found that there were differences in the retinal features that experts considered and their interpretations. It was also found that peripheral retinal features contributed to expert interpretations in

the diagnosis of plus disease (21). Similarly, Keck et al. stated that vascular tortuosity is greater in the periphery than centrally, and that peripheral retinal findings may be important for the diagnosis of plus disease (22). As mentioned in the above studies, in recent years, the view that there is subjectivity in the clinical diagnosis of plus disease and that there are differences between experts has come to the fore. This situation has led to an increase in studies using deep learning models that can yield more objective results. Campbell et al. reported that they achieved 95% diagnostic accuracy in plus disease diagnosis with a computer-based image analysis system developed with a dataset of 77 retinal images, which is similar to experts (79-99%) (9). In our study, we focused on posterior pole images including optic disc and vascular arcades as specified in ICROP criteria for the diagnosis of plus disease. Although we did not make any different interpretations according to arterial tortuosity or venous dilatation in determining plus disease accuracy as Campbell et al. (9) did, we showed that high sensitivity, high specificity and high accuracy can be achieved with the trained models in plus disease diagnosis. In 2018, Brown et al. reported that deep learning algorithms trained to diagnose plus disease on a test set of 100 images achieved 93% sensitivity and 94% specificity, which was equal to or better than human experts (11). On the other hand, Tan et al. showed that the deep learning algorithm they trained could automatically diagnose the disease with high sensitivity (96.6%), high specificity (98%) and high accuracy (97.3%), which is similar to or even higher than the results of our study. They also stated that the algorithm obtained promising results in pre-plus disease detection (23). In our study, we also found that in addition to plus disease diagnosis, pre-plus disease or worse can be diagnosed with high sensitivity, high specificity and high accuracy versus normal. Although the values differed in all 3 algorithms we used, we observed that sensitivity varied between 0.81-0.83, specificity between 0.96-0.99 and accuracy between 0.88-0.91. While VGG16 showed high sensitivity for plus disease, the sensitivity for detecting "pre-plus or worse" versus normal was lower. Missing pre-plus cases can delay closer monitoring and timely intervention, as these cases may progress to plus disease. This reduced sensitivity likely stems from subtle differences between normal and pre-plus cases. Improving the detection of pre-plus disease may require the inclusion of more vascular features, imaging analyses, or peripheral retinal findings. Therefore, the proposed model should be considered a screening tool to support expert clinical examination rather than an independent diagnostic system. The small number of images available for evaluation may have caused differences in the estimated values obtained between studies. Similarly to our study, Mao et al. showed that plus disease can be detected with high accuracy (95.1% sensitivity and 97.8% specificity for plus disease; 92.4% sensitivity and 97.4% specificity for preplus or worse). Moreover, they stated that there were significant changes in pathological features with the quantitative analysis they performed after the treatment of plus disease (24).

Deep learning methods have shown significant progress in medical problems; especially in cases where more subjective diagnoses such as plus disease can be made, it can be a guide through the analysis of images in obtaining more objective results. While the studies support this, there are also studies in the literature where quantitative scoring is used to show the differences in treatment thresholds between examiners in the diagnosis of plus disease (12,24,25). Despite all these results, clinical diagnosis and observation of ROP is always a priority for clinicians.

The retrospective design and small sample size were the most important limitations of the study. In particular, preprocessing the images increased the performance of the algorithms used, while at the same time, it allowed us to perform analysis with small number of images. In addition, the distribution of the groups was determined by the number of fundus images that could be obtained. All of these may have affected model performance and the generalizability of our results. Furthermore, the lack of inability to experiment with different hyperparameters (e.g., learning rate schedulers, dropout variations) to optimize the model's performance may also have impacted our results. In addition, our study focused on the posterior pole, consistent with ICROP definitions of plus disease definitions. However, we acknowledge that peripheral vascular changes may contribute to diagnose and zone 3 cases were excluded, which is a significant limitation. This may reduce generalizability, and future studies using wide-field imaging are needed. On the other hand, the single-center design and lack of external validation limit the generalizability of our findings. Future multi-center studies with independent external validation are needed.

In conclusion, our results showed that DL algorithms can automatically diagnose plus disease in ROP with high sensitivity, high specificity, and high accuracy. Incorporating DL algorithms into clinical diagnosis may contribute to ROP management in the future.

Disclosures

Ethics Committee Approval: This study was conducted following the approval of the Ethical Review Committee of Etlik Zübeyde Hanım Hospital (No: 2024/05, Date: 23/05/2024).

Informed Consent: Written informed consents were obtained from all patients.

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Original Article

Etiological Spectrum and Visual Outcomes of Spontaneous Vitreous Hemorrhage

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Abstract

Objectives: To evaluate the age-related etiological spectrum and visual outcomes of patients presenting with spontaneous vitreous hemorrhage (VH) at a tertiary eye emergency department.

Methods: This single-center retrospective cohort study reviewed the medical records of 55,107 patients who presented to a tertiary referral hospital between January 2018 and December 2024. A total of 804 eyes of 804 patients with a first episode of spontaneous vitreous hemorrhage and at least 12 months of follow-up were included. Etiology was determined by clinical examination, imaging methods, and diagnostic pars plana vitrectomy (PPV) when required. Patients were categorized into pediatric (<18 years), adult (18–65 years), and elderly (>65 years) groups. Best-corrected visual acuity (BCVA) at presentation and at 12-month follow-up was analyzed. Visual outcomes were compared between the early (≤3 months) and delayed (>3 months) vitrectomy groups.

Results: The incidence of spontaneous VH among emergency presentations was 1.46%. Male patients constituted 60.57% of the cohort. Retinopathy of prematurity was the most common etiology in pediatric patients, whereas proliferative diabetic retinopathy predominated in the adult and elderly groups. Mean BCVA improved from 1.54±0.63 logMAR at presentation to 0.38±0.39 logMAR at 12 months ($p<0.001$). Significant visual improvement was observed in all age groups ($p<0.001$). Diagnostic PPV was performed in 27% of eyes. Visual gain was greater in the early vitrectomy group than in the delayed vitrectomy group (0.58±0.25 vs 0.44±0.31 logMAR; $p=0.02$).

Conclusion: The etiological spectrum of spontaneous VH varies according to age. Significant visual improvement can be achieved with appropriate medical and surgical treatment. Early PPV in selected cases may provide superior visual recovery compared with delayed intervention.

Keywords: Diabetic retinopathy, Pars plana vitrectomy, Retinopathy of prematurity, Vitreous hemorrhage

Introduction

Vitreous hemorrhage (VH) is a common and potentially vision-threatening condition that leads to sudden vision loss and is characterized by the accumulation of blood in the vitreous cavity (1). The reported incidence of spontaneous VH varies across populations and geographic regions. Lindgren et al. reported an annual incidence of approximately 7 cases per 100,000 individuals, whereas Wang et al. reported a substantially higher incidence of 4.8 cases per 10,000 person-years in a population-based study conducted in Taiwan (2,3). VH has a wide range of etiologies, with the prevalence of underlying causes differing according to the characteristics of the study population. The most common etiologies

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consistently include proliferative diabetic retinopathy (PDR), posterior vitreous detachment (PVD) with or without an associated retinal tear, and ocular trauma, which together account for approximately 59–88.5% of all cases (4). Less frequent causes include various retinal vascular and systemic conditions, including retinal vein occlusion (RVO), retinal vasculitis, proliferative sickle cell retinopathy, retinal arterial macroaneurysm rupture, and Valsalva retinopathy (5–8). In rarer instances, VH may occur secondary to subarachnoid hemorrhage (Terson syndrome), inherited or developmental retinal disorders such as X-linked retinoschisis, retinopathy of prematurity (ROP), and familial exudative vitreoretinopathy (FEVR), as well as inflammatory conditions, blood dyscrasias, coagulation disorders, and neovascular age-related macular degeneration. Epidemiological data show that VH is more prevalent with increasing age, exhibits a male predominance, and may be linked to the use of anticoagulants (2).

Clinically, VH typically presents with sudden, painless visual impairment ranging from mild visual haze to severe vision loss (9,10). From a pathophysiological perspective, VH most commonly results from either mechanical disruption of normal retinal vessels or hemorrhage from fragile pathological neovascular structures extending into the vitreous cavity. Thus, VH represents a terminal common pathway for several ocular disorders, each with significantly different prognostic and therapeutic implications.

Although the etiological spectrum of VH is well documented, research specifically addressing patients presenting to eye emergency departments is limited, especially in tertiary referral centers. In the acute setting, extensive VH often obstructs sufficient fundus visibility, hindering timely etiological assessment and treatment decisions. The distribution of underlying causes and associated visual outcomes may differ substantially among emergency presentations. Therefore, the present study aimed to evaluate the etiological spectrum and visual outcomes of patients presenting with spontaneous VH to a tertiary referral hospital. By analyzing a large, single-center retrospective cohort, we sought to identify the most common underlying diagnoses and assess changes in visual acuity following medical and surgical management.

Methods

Study Design and Participants

For this retrospective cohort study, the medical records of 55,107 patients who presented to the Emergency Department of Beyoğlu Eye Training and Research Hospital between January 2018 and December 2024 were reviewed. Among these patients, 804 eyes of 804 patients who were referred to the Retina Department with a diagnosis of VH and followed for at least one year were included in the study. The study protocol was approved by the University of Health Sciences Taksim Training and Research Hospital Ethics Committee (decision number: 97; date: January 7, 2026) and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were included if they (1) presented with a first episode of spontaneous VH and (2) had a minimum follow-up of 12 months. Patients were excluded if they had (1) a history of ocular or head trauma; (2) corneal pathology that could affect best-corrected visual acuity; (3) a history of glaucoma; (4) a previous history of VH; (5) iatrogenic or postoperative VH, including eyes with prior vitreoretinal surgery and/or previous retinal laser photocoagulation; or (6) inadequate medical records to determine key variables or outcomes.

At each visit, all measurements and imaging evaluations were performed by experienced ophthalmologists. The ophthalmologic examination included slit-lamp biomicroscopy, measurement of best-corrected visual acuity (BCVA) using a Snellen chart, intraocular pressure (IOP, mmHg) assessment by Goldmann applanation tonometry, and dilated fundus evaluation using a 90-diopter lens. When the fundus could not be adequately visualized due to dense VH, B-scan ultrasonography (E-Z Scan AB5500+, X9Ware LLC, USA) was performed to evaluate the posterior segment, including the presence of retinal detachment or retinal tears. Orbital and/or cranial imaging was obtained when clinically indicated to evaluate suspected associated orbital or intracranial pathology. When the cause of VH could not be ascertained using imaging techniques and the hemorrhage persisted during follow-up, 23-gauge pars plana vitrectomy (PPV) was performed for both diagnostic and therapeutic purposes. All vitreoretinal procedures were performed by experienced retina specialists. For subgroup analysis, PPV timing was categorized as early (≤3 months) or delayed (>3 months). As reported in the literature, there is no universally accepted temporal definition for early versus late PPV in VH(1). Different thresholds, such as 3 or 6 months, have been used in previous studies (11–13).

Given the age-dependent differences in VH etiology, patients were categorized into three age groups for analysis: pediatric (<18 years), adult (18–65 years), and elderly (>65 years). Objective refraction (D) was measured using an automated refractometer (Canon RK-F2, USA). Additional imaging modalities, such as optical coherence tomography (OCT; Heidelberg Spectralis, Germany), fundus fluorescein angiography (FA) and indocyanine green angiography (ICGA; Heidelberg Engineering, Heidelberg, Germany), and swept-source optical coherence tomography angiography (OCTA; DRI Triton, Topcon, Japan), were obtained as clinically indicated after clearance of the VH to determine the underlying etiology. OCT was primarily used for macular structural evaluation and detection of macular edema and epiretinal

membrane (ERM), OCTA for assessment of macular neovascularization (MNV), FA for evaluation of retinal vascular abnormalities such as RVO and PDR, and ICGA particularly for characterization of polypoidal choroidal vasculopathy and other choroidal vascular pathologies. According to the identified diagnosis, appropriate treatments, including intravitreal anti-VEGF injections and laser photocoagulation, were administered.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test, together with evaluation of skewness and kurtosis values (14). Continuous data are reported as mean±standard deviation, whereas categorical variables are expressed as frequencies and percentages. Visual acuity measurements obtained using the Snellen chart were converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. Changes between presentation and 12-month follow-up measurements were analyzed using paired-samples t-tests for normally distributed variables and Wilcoxon signed-rank tests for variables with non-normal distributions. Comparisons between two independent groups were conducted using the independent-samples t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Comparisons involving more than two independent groups were performed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. When appropriate, post hoc analyses were conducted with Bonferroni correction. Categorical data were evaluated using the chi-square test. A p-value less than 0.05 was considered statistically significant.

Results

A total of 804 eyes of 804 patients with spontaneous VH were included in the final analysis. The incidence of spontaneous VH among emergency department presentations was 1.46%. Of the entire cohort, 487 patients (60.57%) were male and 317 (39.43%) were female. Male predominance was observed across all age groups, with males representing 62.96% of the pediatric group, 59.16% of the adult group, and 61.49% of the elderly group. Table 1 shows the etiological distribution of all eyes, with PDR identified as the leading cause. The etiological spectrum was further investigated based on age group stratification. In patients under 18 years of age, the most common cause was ROP (Table 2). In both the adult (18–65 years) and elderly (>65 years) groups, PDR was the predominant etiology (Tables 3 and 4).

The mean age of the study population was 65.47±14.08 (5–89) years. The mean age was 14.83±3.06 (5–17) years in the pediatric group, 57.41±6.93 (19–64) years in the adult group, and 74.59±5.84 (66–89) years in the elderly group. Oral anticoagulant use was documented in 87 adults (26.13%) and 181 elderly patients (40.77%). Diagnostic PPV was performed in 217 eyes (27%) in which the etiology of VH could not be determined by initial fundus examination and B-scan ultrasonography and in which the hemorrhage failed to resolve during follow-up. The mean interval from initial diagnosis to PPV was 3.47±1.72 (1–6) months. In cases

Table 1. Etiological distribution of spontaneous vitreous hemorrhage (n=804 eyes)

Etiology	n	%
Proliferative diabetic retinopathy	409	50.87
Retinal detachment	105	13.06
Retinal vein occlusion	83	10.32
Retinal tear / acute posterior vitreous detachment	70	8.71
Hypertensive retinopathy	37	4.60
Retinal arterial macroaneurysm rupture	24	2.99
Polypoidal choroidal vasculopathy	9	1.12
Neovascular age-related macular degeneration	7	0.87
Endogenous endophthalmitis	7	0.87
Retinopathy of prematurity	7	0.87
Valsalva retinopathy	6	0.75
Familial exudative vitreoretinopathy	4	0.50
Retinal vasculitis	4	0.50
Retinal arteriovenous malformation	2	0.25
Sickle cell retinopathy	1	0.12
Idiopathic	29	3.61
Total	804	100.00

Table 2. Etiological distribution of spontaneous vitreous hemorrhage (<18 years) (n=27 eyes)

Etiology	n	%
Retinopathy of prematurity	7	25.93
Familial exudative vitreoretinopathy	3	11.11
Retinal tear / acute posterior vitreous detachment	3	11.11
Proliferative diabetic retinopathy	2	7.41
Retinal detachment	2	7.41
Endogenous endophthalmitis	2	7.41
Valsalva retinopathy	2	7.41
Retinal vasculitis	1	3.70
Retinal arteriovenous malformation	1	3.70
Idiopathic	4	14.81
Total	27	100.00

Table 3. Etiological distribution of spontaneous vitreous hemorrhage (18 - 65 years) (n=333 eyes)

Etiology	n	%
Proliferative diabetic retinopathy	167	50.15
Retinal detachment	51	15.32
Retinal tear / acute posterior vitreous detachment	28	8.41
Retinal vein occlusion	26	7.81
Hypertensive retinopathy	15	4.50
Retinal arterial macroaneurysm rupture	13	3.90
Polypoidal choroidal vasculopathy	6	1.80
Valsalva retinopathy	4	1.20
Neovascular age-related macular degeneration	2	0.60
Endogenous endophthalmitis	2	0.60
Retinal vasculitis	3	0.90
Familial exudative vitreoretinopathy	1	0.30
Retinal arteriovenous malformation	1	0.30
Sickle cell retinopathy	1	0.30
Idiopathic	13	3.90
Total	333	100.00

in which VH resolved during follow-up, appropriate patients underwent laser photocoagulation and/or intravitreal anti-VEGF injections based on the underlying etiology.

In all patients, mean BCVA was 1.54±0.63 logMAR at presentation and improved to 0.38±0.39 logMAR at 12 months (p<0.001). In the pediatric group, mean BCVA at presentation was 1.12±0.43 logMAR and improved to 0.44±0.37 logMAR at 12 months (p<0.001). In the adult group, mean BCVA improved from 1.21±0.45 logMAR at presentation to 0.37±0.41 logMAR at the 12-month follow-up (p<0.001). In the elderly group, mean BCVA was 1.82±0.63 logMAR at presentation and improved to 0.39±0.37 logMAR at 12 months (p<0.001). No significant difference in IOP was found between presentation and the 12-month follow-up in all patients or among age subgroups (p>0.05 for all). Among the 217 eyes that underwent PPV, early vitrectomy (≤3 months) was performed in 80 eyes (36.87%), whereas delayed vitrectomy (>3 months) was performed in 137 eyes (63.13%). The mean BCVA gain (ΔlogMAR) was significantly greater in the early vitrectomy group than in the delayed vitrectomy group (0.58±0.25 vs 0.44±0.31, p=0.02).

Table 4. Etiological distribution of spontaneous vitreous hemorrhage (>65 years) (n=444 eyes)

Etiology	n	%
Proliferative diabetic retinopathy	240	54.05
Retinal detachment	52	11.71
Retinal vein occlusion	57	12.84
Retinal tear / acute posterior vitreous detachment	39	8.78
Hypertensive retinopathy	22	4.95
Retinal arterial macroaneurysm rupture	11	2.48
Polypoidal choroidal vasculopathy	3	0.68
Neovascular age-related macular degeneration	5	1.13
Endogenous endophthalmitis	3	0.68
Idiopathic	12	2.70
Total	444	100.00

In the pediatric group, ERM developed in 2 eyes (7.4%) during follow-up. In the adult group, during the 12-month follow-up, 36 of 167 eyes with PDR (21.6%) required intravitreal treatment for macular edema, including anti-VEGF agents or dexamethasone implants. Additionally, intravitreal anti-VEGF injection was required in 4 of 6 eyes with polypoidal choroidal vasculopathy (PCV) (66.7%) and in 1 of 2 eyes with neovascular age-related macular degeneration (nAMD) (50%) due to MNV activity. In the elderly group, during the 12-month follow-up, 63 of 240 eyes with PDR (26.3%) and 14 of 57 eyes with RVO (24.6%) required intravitreal treatment for macular edema, including anti-VEGF agents or dexamethasone implants. Additionally, intravitreal anti-VEGF injection was required in 1 of 3 eyes with PCV (33.3%) and in 4 of 5 eyes with nAMD (80.0%) due to MNV activity.

Discussion

In this large single-center retrospective cohort, we evaluated the etiological spectrum and visual outcomes of spontaneous VH presenting to a tertiary eye emergency department. This study provides real-world data on the distribution of underlying causes across different age groups.

Previous epidemiological studies have described a male predominance in spontaneous VH. Otabor-Olubor et al. found that 73% of patients presenting with VH in a tertiary hospital setting were male, corresponding to a male-to-female ratio of 1:0.37 (15). In a large population-based study from Taiwan, Wang et al. demonstrated a higher incidence of VH in males than in females and identified male sex as an independent risk factor (2). Sativada et al. found a pronounced male predominance in VH, with males comprising 76.19% of their study population (16). In line with previous reports, a male predominance was also observed in our study. Previous studies have indicated that male sex is a risk factor for the development of ROP (17–19). The male predominance in the pediatric VH subgroup may be attributed to the prevalence of ROP as the primary cause.

The etiological spectrum of VH is known to vary according to patient age and underlying systemic conditions.

Previous literature has shown that PDR, PVD-related retinal breaks, and ocular trauma are the leading causes of VH, collectively encompassing the majority of cases in most studies (10). In particular, PDR has been repeatedly reported as the leading etiology of spontaneous VH (2,3,15). Consistent with these reports, PDR was the leading cause of VH in both the adult and elderly subgroups in our cohort. This finding likely reflects the high burden of diabetes-related microvascular disease in older populations and underscores the continued role of PDR as a principal cause of vision-threatening VH in real-world clinical practice.

Visual acuity outcomes represent the most clinically relevant endpoint in VH, as final vision largely depends on both the underlying etiology and the timeliness of intervention. Previous studies have reported significant visual improvement following appropriate medical or surgical management of spontaneous VH (20,21). In our study, BCVA improved significantly from presentation to 12-month follow-up in all patients, as well as across all age subgroups, indicating that substantial visual recovery can be achieved. Notably, elderly patients presented with worse baseline vision, yet demonstrated comparable visual gains after treatment. These findings indicate that prompt etiological identification and customized interventions, such as laser photocoagulation, intravitreal anti-VEGF injection, and PPV when necessary, facilitate significant visual rehabilitation in spontaneous VH.

The optimal timing of PPV in spontaneous VH remains a subject of ongoing debate, particularly in eyes in which the underlying etiology cannot be promptly identified or VH fails to clear spontaneously. Previous studies have suggested that early vitrectomy may facilitate faster visual rehabilitation, reduce the risk of secondary complications, and allow earlier treatment of the primary retinal pathology (13,22). Nevertheless, controversy remains concerning the optimal timing for surgical intervention in VH. A systematic review reported that no clear consensus exists on the optimal timing of PPV for VH (1). Fassbender et al. reported significant visual improvement in both early and delayed vitrectomy groups, with no significant difference in visual outcomes between the two approaches in PDR-associated VH (23). In our study, early vitrectomy was associated with significantly greater visual gain than delayed surgery. This finding may be attributed to the adverse effects of prolonged VH, which can result in retinal toxicity from hemoglobin degradation products, secondary vitreoretinal traction, ERM formation, and delayed intervention for the underlying pathology. Despite the greater visual gain observed with early PPV, the proportion of patients undergoing delayed PPV was higher in our study. In routine clinical practice, delayed PPV may be preferred in selected cases to allow the possibility of spontaneous clearance of VH and to improve visualization of the underlying retinal pathology before surgery. In addition, factors such as surgical scheduling, clinical workload in high-volume referral centers, patient comorbidities, and the severity of visual impairment may also influence the timing of surgery in real-world settings.

This study has several limitations. First, the retrospective design may introduce both selection bias and information bias inherent to observational studies and may limit control over potential confounding variables. Second, some etiological subgroups, particularly pediatric cases and rare causes of VH, included relatively small numbers of patients, which may have reduced the statistical power for subgroup analyses. Third, due to the real-world nature of the study, the timing of PPV was determined according to the individual clinical judgment of the treating retina specialists rather than a predefined standardized protocol, which may introduce potential selection bias and confounding when comparing early and delayed PPV groups.

In conclusion, this large real-world cohort shows that the etiological spectrum of spontaneous VH presenting to a tertiary eye hospital emergency department varies substantially by age group, with ROP predominating in pediatric patients and PDR as the leading cause in adult and elderly populations. Significant visual improvement can be achieved following appropriate medical and surgical management. Moreover, our findings suggest that early PPV in selected cases of persistent VH may provide superior visual recovery compared with delayed intervention. These results emphasize the importance of timely etiological assessment and individualized treatment strategies in optimizing visual outcomes in spontaneous VH.

Disclosures

Ethics Committee Approval: This study was approved by The University of Health Sciences Taksim Training and Research Hospital Ethics Committee (decision number: 97; date: January 7, 2026).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there are no conflicts of interest

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Original Article

Comparison of Patients with Diabetic Macular Edema Undergoing Early versus Late Switch from Intravitreal Anti-VEGF Therapy to Dexamethasone Implant

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Abstract

Objectives: To compare anatomical and functional outcomes in patients with diabetic macular edema who exhibited a suboptimal response to intravitreal anti-VEGF therapy and underwent early (<6 months) versus late (≥6 months) switch to an intravitreal dexamethasone implant.

Methods: This retrospective comparative study included 141 eyes of 141 patients with diabetic macular edema. Patients received at least three consecutive anti-VEGF injections without adequate anatomical or functional response and were subsequently switched to a dexamethasone implant. Patients were divided into two groups: early switch (<6 months) and late switch (≥6 months). Best-corrected visual acuity, central macular thickness, optical coherence tomography biomarkers, intraocular pressure, lens status, number of injections, and complications were analyzed.

Results: Of 141 patients (79 females, 62 males; mean age 65.3±8.9 years), 49 were in the early switch group and 92 were in the late switch group. At baseline, best-corrected visual acuity was marginally better in the late switch group (p=0.049), while baseline central subfield thickness was comparable (p=0.35). After switching, both groups showed a significant reduction in central subfield thickness (p<0.01), with no difference between the groups (p=0.58). Best-corrected visual acuity improved significantly in both groups; however, visual gain was greater in the early switch group (p=0.038). The mean number of total intravitreal injections was significantly higher in the late switch group (p<0.01). Mean intraocular pressure increased from 16.3 to 18.0 mmHg in both groups (p<0.01), with no intergroup difference. Thirty-one patients required cataract surgery during follow-up, without correlation with switch timing. Optical coherence tomography biomarkers revealed that patients with ellipsoid zone disruption had poorer BCVA outcomes, while those with subfoveal serous detachment exhibited greater central subfield thickness reduction (p<0.05).

Conclusion: Early switch from anti-VEGF to a dexamethasone implant in refractory diabetic macular edema provides superior functional outcomes and reduces treatment burden compared with late switch, despite similar anatomical improvements.

Keywords: Anti-VEGF, dexamethasone implant, diabetic macular edema, switch

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Introduction

Diabetic macular edema (DME) is a leading cause of visual impairment among patients with diabetes, affecting approximately 27 million individuals worldwide(1,2). The underlying pathology involves disruption of the blood-retinal barrier and accumulation of extracellular fluid in the macula, resulting in increased central retinal thickness and reduced visual acuity. Intravitreal (IV) anti-vascular endothelial growth factor (anti-VEGF) agents (ranibizumab, aflibercept, bevacizumab, faricimab, and brolucizumab) are well-established first-line treatments, with numerous randomized clinical trials demonstrating their efficacy in improving visual acuity and reducing macular thickness (3–5).

However, a substantial proportion of patients exhibit a suboptimal response to anti-VEGF therapy (6). This lack of response suggests that non-VEGF inflammatory pathways contribute significantly to DME pathogenesis (7). In this context, the IV dexamethasone implant (0.7 mg; Ozurdex®, Allergan Inc., Irvine, CA, USA) has emerged as an alternative treatment option in such cases. The dexamethasone implant suppresses a broad range of inflammatory mediators, thereby improving DME outcomes. These effects have been demonstrated in both treatment-naïve and resistant cases (8).

Nevertheless, despite its efficacy, the dexamethasone implant is mostly preferred as a second-line therapy due to potential complications such as cataract formation and intraocular pressure elevation. Still, considering that anti-VEGF agents and corticosteroids target different biological pathways, corticosteroid therapy may be beneficial in patients with an insufficient response to anti-VEGF treatment (9).

Currently, the optimal timing of switching from anti-VEGF to corticosteroid therapy in clinical practice remains controversial. Some evidence suggests that early switching may yield better outcomes by limiting the progression of retinal damage.

This study aimed to compare anatomical and functional outcomes between patients with refractory DME undergoing an early (<6 months) versus late (≥6 months) switch from anti-VEGF therapy to a dexamethasone implant.

Methods

This retrospective comparative clinical study included patients diagnosed with DME and treated between 2016 and 2023 in the ophthalmology department of our institution. The study was approved by the local ethics committee of our hospital (date: November 7, 2023; approval code: E-48670771-514.99-228766276) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Population

Patients diagnosed with type 2 diabetes who received at least three intravitreal anti-VEGF injections (ranibizumab, aflibercept, or bevacizumab) but showed insufficient anatomical or functional response and were subsequently treated with an IV dexamethasone implant were included in the study.

Inclusion Criteria

- Age ≥18 years
- Diagnosis of diabetic macular edema
- At least three consecutive doses of intravitreal anti-VEGF injections
- Insufficient response to anti-VEGF treatment (no increase in best-corrected visual acuity [BCVA] or no significant reduction in central subfield thickness [CST])
- Minimum follow-up of 6 months

Exclusion Criteria

- History of vitreoretinal surgery
- Poor-quality OCT imaging due to media opacities
- Tractional macular edema secondary to proliferative diabetic retinopathy
- Retinal or optic nerve diseases (e.g., neovascular age-related macular degeneration, glaucoma)

Grouping

- Patients were classified based on switch timing:
- Early switch: Patients who received a dexamethasone implant before 6 monthS
- Late switch: Patients who received a dexamethasone implant at or after 6 months

Treatment Protocol

All IV injections were performed under aseptic conditions using a 30-gauge needle via the inferotemporal quadrant. The dexamethasone implant was administered in accordance with the manufacturer's instructions. After the procedure, patients were treated with topical antibiotics for one week. All treatment decisions were made by the same retina specialists.

Data Collection and Follow-up

The collected data included:

- Demographic characteristics (age, sex, systemic comorbidities)
- History of panretinal photocoagulation
- BCVA, measured using a Snellen chart
- CST, measured by spectral-domain optical coherence tomography (Heidelberg Engineering® SD-OCT)
- OCT findings: epiretinal membrane (ERM), pearl necklace sign, subfoveal hard exudates, hyperreflective dots (HRD), disorganization of the retinal inner layers (DRIL), type of edema, status of the ellipsoid zone

(EZ), serous macular detachment (SMD), and intraretinal hyperreflectivity
- Intraocular pressure (IOP), measured by Goldmann applanation tonometry
- Lens status (pseudophakic/phakic)
- Type and number of anti-VEGF agents
- Timing and number of dexamethasone implants
- Duration of follow-up

Assessment Timepoints:
- Baseline BCVA and CST
- BCVA and CST after anti-VEGF therapy (pre-switch)
- BCVA and CST at the last visit following dexamethasone treatment
- All complications during at least 6 months of follow-up (cataract progression, IOP elevation)

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean±standard deviation (SD). Intergroup comparisons were conducted using independent t-tests or Mann–Whitney U tests. Categorical variables were compared using chi-square tests. Repeated-measures ANOVA was used to assess longitudinal changes in BCVA and CST. Correlations were analyzed using Pearson or Spearman tests. A p-value <0.05 was considered statistically significant.

Results

A total of 141 eyes from 141 patients (79 females, 62 males; mean age: 65.30±8.89 years) were included. According to the timing of the switch to a dexamethasone implant, 49 patients were in the early switch group, while 92 were in the late switch group. At baseline, BCVA comparison showed that the late switch group had marginally better vision than the early switch group (p=0.049). Baseline CST was similar between the two groups (p=0.35). Descriptive characteristics are summarized in Table 1.

The mean BCVA and CST at the last visit before the switch were comparable (p=0.91 and p=0.66, respectively). Before the switch, bevacizumab was significantly more commonly used in the early switch group (p<0.01), whereas no significant difference was found among anti-VEGF agents in the late switch group (p=0.688). Following subgroup analysis stratified by the pre-switch anti-VEGF agent, after adjusting for baseline BCVA, early versus late switching was not independently associated with visual gain in any subgroup (bevacizumab: p=0.338; aflibercept: p=0.670; ranibizumab: p=0.904).

The mean total follow-up duration was 34.88±2.40 months. The number of dexamethasone implants was similar between the two groups (p=0.096), whereas the total number of intravitreal injections was significantly higher in the late switch group (p<0.01).

Analysis of CST changes revealed a significant reduction in both groups (p<0.01), with no significant difference between the groups (p=0.58) (Fig. 1). Regarding BCVA changes, visual gain increased significantly in both groups; however, the early switch group achieved statistically greater visual improvement than the late switch group (p=0.038) (Fig. 2).

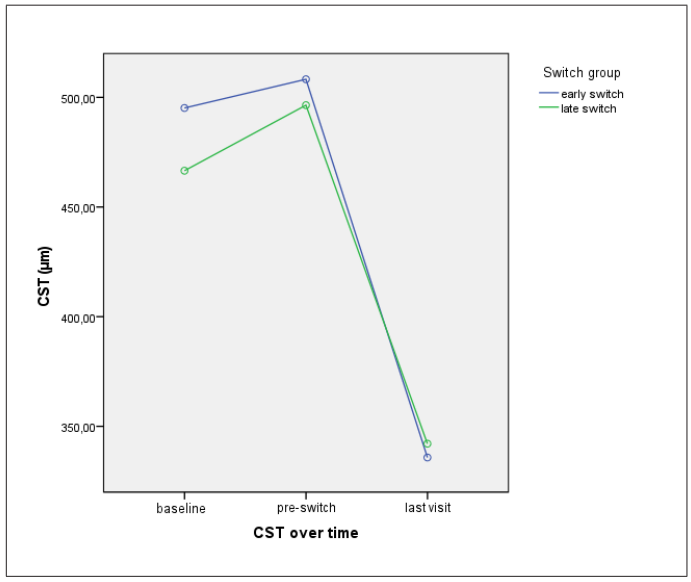

Figure 1. Central subfield thickness changes over time by groups.

Table 1. Descriptive istatistics of the groups

	Early switch	Late switch	p
Age (mean.±SD, years)	64.92±9.77	65.50±8.43	0.71
Gender (female, %)	55%	56%	0.87
Baseline BCVA (mean.±SD, decimal)	0.25±0.22	0.34±0.28	**0.049**
Baseline CST(mean.±SD, µm)	495.18±186.79	466.57±168.9	0.35
Baseline IOP(mean.±SD, mmHg)	16.35±3	16.30±3.6	0.94
Baseline lens status (phakic, %)	73%	80%	0.34

BCVA: Best-corrected visual acuity; CST: Central subfield thickness; IOP: Intraocular pressure; SD: Standard deviation

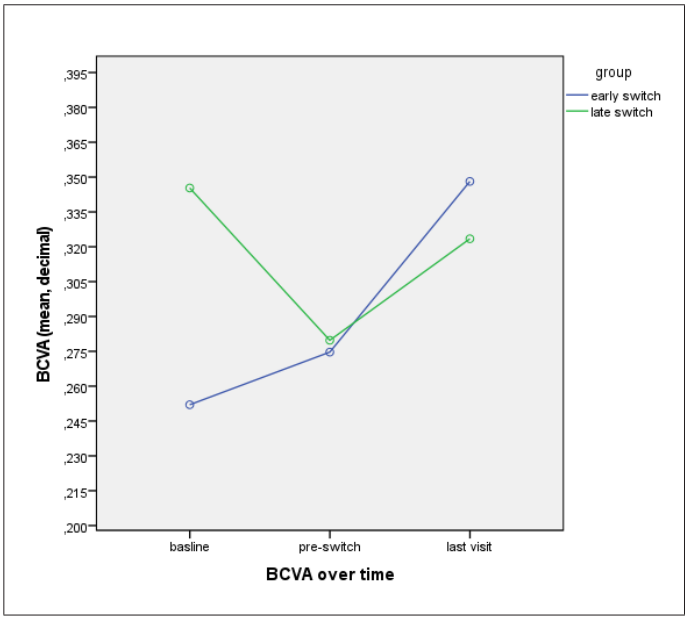

Figure 2. Best-corrected visual acuity changes over time by groups.

At the last visit, BCVA was negatively correlated with pre-switch CST and the total number of injections and positively correlated with pre-switch BCVA (p<0.01).

Mean IOP increased significantly from 16.32 mmHg to 18.00 mmHg in both groups, with no intergroup difference (p=0.98). None of the patients required glaucoma surgery, and there was no difference between the groups in the use of anti-glaucomatous medications (p=0.20). During follow-up, 31 patients underwent cataract surgery, but no correlation was observed with the timing of the switch (p=0.07). The values at the end of follow-up are summarized in Table 2.

During follow-up, five patients underwent vitrectomy, with no association with the groups (p=0.554). No cases of post-injection endophthalmitis were reported.

OCT biomarker analysis revealed that patients with pre-switch EZ damage (Fig. 3) had lower mean BCVA at both the pre-switch and last visits (p=0.011 and p=0.012, respectively). Patients with pre-switch SMD (Fig. 4) had higher pre-switch CST values, whereas their mean CST at the last visit was lower (p<0.01 and p=0.023, respectively). Patients with pre-switch ERM had higher mean CST at the last visit (p=0.06). No significant correlations were found with other OCT parameters.

OCT biomarkers were evaluated at baseline, pre-switch, and final visits. At baseline, the late switch group demonstrated a higher frequency of intracystic hyperreflectivity (Fig. 5) (p=0.12). No significant differences were observed between the two groups for the other parameters at any time.

Discussion

Although focal/grid laser photocoagulation was used for DME treatment in the 1980s, it has been largely abandoned due to side effects such as choroidal neovascularization and subretinal fibrosis. Intravitreal anti-VEGF therapy has since provided significant anatomical and functional improvements (10–12). However, persistent DME in nearly 40% of patients suggests that VEGF-independent inflammatory mechanisms play a key role in disease progression (13,14). In this context, corticosteroid-based therapies, including dexamethasone implants, as well as subthreshold laser and surgical procedures, are among the other treatment options for DME (14).

The role of inflammatory mechanisms in persistent DME has increasingly been recognized, providing a rationale for the development of intravitreal corticosteroid therapies (15). Corticosteroids inhibit the expression of proinflammatory cytokines and chemokines, reduce retinal neovascularization and vascular permeability, and provide significant anatomical and functional improvements in patients with DME (16,17). Furthermore, they have been reported as alternative or adjunctive treatment options in patients resistant to anti-VEGF agents (18).

Among corticosteroid treatment options, sub-Tenon and intravitreal triamcinolone acetonide, as well as intravitreal fluocinolone acetonide implants, are available; however, in Türkiye, the intravitreal dexamethasone implant is generally preferred (19). Despite broad agreement on anti-VEGF agents as first-line treatment, the optimal timing for switching to corticosteroids remains uncertain.

Table 2. Values by the groups at the end of the follow-up

	Early switch	Late switch	p
Number of injections (mean±SD)	5.06±1.43	8.08±3.49	**<0.01**
Number of dexamethasone implants (mean±SD)	2.12±1.23	2.58±1.96	0.096
BCVA at end of the follow-up (mean±SD, decimal)	0.34±0.30	0.32±0.30	**0.038**
CST at end of the follow-up (mean±SD, μm)	335.82±116.54	342.12±126.39	0.58
IOP at the end of the follow-up (mean±SD, mmHg)	18.04±5	17.96±4.4	0.98
Lens status at the end of the follow-up (phakic, %)	61%	53%	0.07

BCVA: Best-corrected visual acuity; CST: Central subfield thickness; IOP: Intraocular pressure; SD: Standard deviation.

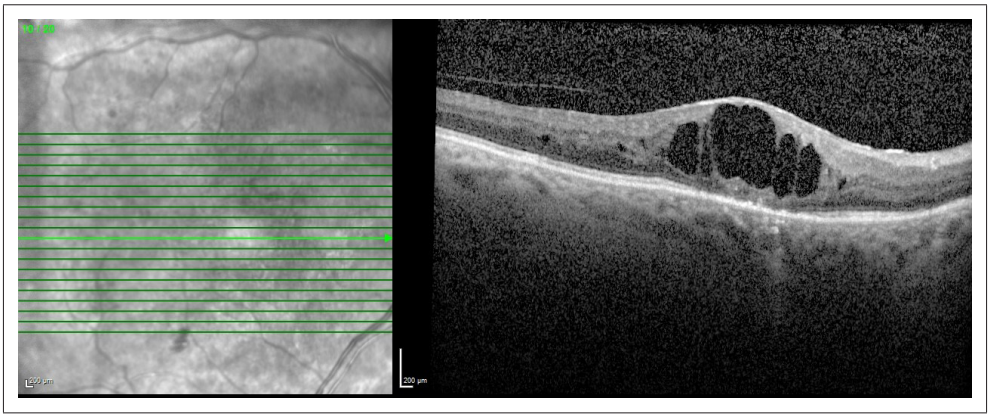

Figure 3. Ellipsoid zone dysruption.

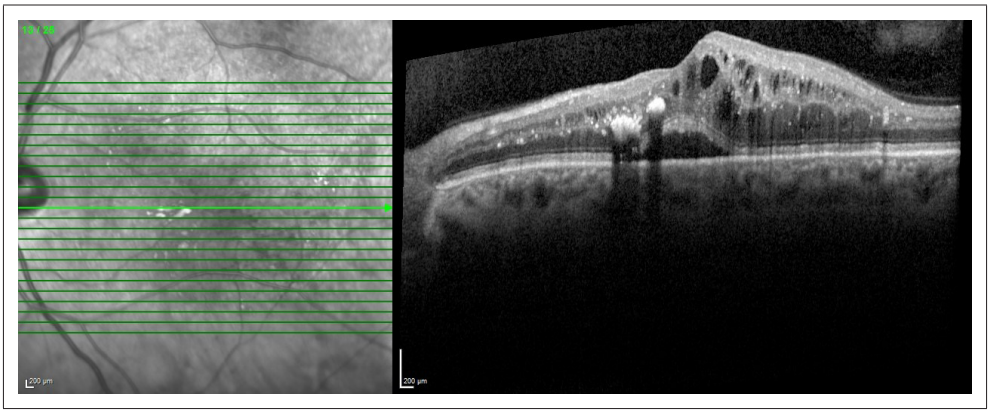

Figure 4. Serous macular detachment.

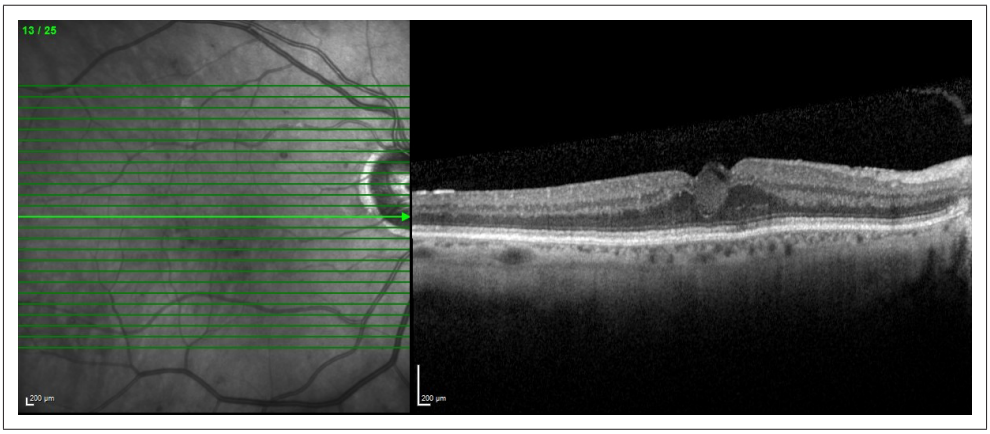

Figure 5. Intracystic hyperreflecitivity.

In 2019, Busch et al. published a retrospective study evaluating the 2-year results of 87 patients with DME. Among them, 44 received only anti-VEGF treatment, 14 switched to dexamethasone in the second year, and 29 underwent early switch to dexamethasone in the first year. Comparison of the 2-year outcomes showed that the anti-VEGF-only group did not achieve significant anatomical or functional improvement after the loading dose, whereas the early switch group maintained visual acuity and continued to show CST reduction by the second year. In the late switch group, significant functional and anatomical improvement was observed between months 12 and 24. Both steroid groups had similar visual gains at the 24th month, while area-under-the-curve analysis demonstrated superior outcomes in the early switch group (20).

Similarly, in 2020, Hernández Martínez et al. reported that 2-year visual acuity outcomes were better in the ear-

ly switch group (21). In the same year, Demir et al. found that 12-month outcomes were similar between the early and late switch groups; however, at 6 months, the early switch group had better BCVA and CST results (22). According to Ruiz-Medrano et al. (2021), similar findings were observed, with superior outcomes in the early switch group (23). The multicenter IRGREL-DEX study also confirmed that dexamethasone provides better responses in treatment-naïve eyes (24).

In 2024, Raizada et al. included 105 eyes of 77 patients with resistant DME in a retrospective study comprising three groups: Group I switched to a steroid implant after 3 anti-VEGF injections, Group II after 4–6 injections, and Group III after more than 6 injections. Post-switch visual gain was highest in Group II. They attributed the reduced visual gain in resistant DME compared with treatment-naïve eyes to prolonged capillary ischemia causing photoreceptor damage (25).

In our study, we compared early (<6 months) and late (≥6 months) switch to a dexamethasone implant in patients with DME. The results showed that visual acuity gain was greater in the early switch group, emphasizing the importance of early intervention to prevent permanent retinal damage. However, patients in the late switch group had better baseline visual acuity, which may have limited the magnitude of potential visual improvement due to a ceiling effect.

In 2025, Çakmak et al. conducted a retrospective study in which patients were divided into two groups: the adjuvant group continued ranibizumab after dexamethasone, while the switch group continued with dexamethasone alone. Comparison of BCVA and CST values at months 9 and 12 showed that the switch group achieved superior outcomes with fewer injections (26).

Our results align with these findings, demonstrating significantly better BCVA improvement in the early switch group. Nevertheless, both groups achieved similar CST reduction. This finding indicates that both anti-VEGF agents and corticosteroids have the capacity to provide anatomical improvement. However, differences in visual acuity suggest that changes in retinal microstructure (e.g., EZ damage or presence of SMD) may affect treatment response.

A 2024 review by Vitiello et al. compared OCT biomarkers in anti-VEGF and dexamethasone treatments and found that patients with large intraretinal cysts, DRIL, HRDs, and chronic DME with SMD responded better to dexamethasone (27). Cavalleri et al. (2019) observed that early switch from ranibizumab to dexamethasone resulted in the greatest visual gain in patients with EZ damage, no DRIL, and a higher number of HRDs (28).

The need for multiple intravitreal injections in patients with DME reduces treatment adherence and increases the burden on both patients and healthcare systems. Therefore, there is a growing need for therapies with fewer injections and longer treatment intervals. In this study, early switching reduced the total number of injections, likely reflecting the longer duration of action of dexamethasone implants. Similarly, a 2022 cost-effectiveness study by Moreno and Medrano found that early switch to dexamethasone was more cost-effective than extending anti-VEGF therapy to 6 months in patients with a suboptimal response (29).

Dexamethasone implant-related complications in our study included IOP elevation and cataract progression; however, none of these significantly affected treatment continuation, and all were manageable. This supports corticosteroid therapy as a safe alternative. A 2023 review by Taloni et al. recommended a dexamethasone implant as the preferred treatment in pseudophakic and vitrectomized eyes and as a strong alternative in phakic patients undergoing cataract surgery, in DME cases with a high inflammatory component, and in patients unresponsive to anti-VEGF therapy. In persistent and severe cases, combination therapy with anti-VEGF is suggested (30).

Our study has limitations, including its retrospective design and modest sample size. Additionally, the type and duration of diabetes, as well as HbA1c levels and insulin use, were not recorded. An additional group of patients switching to dexamethasone after 3–6 anti-VEGF injections could also have been established.

Conclusion

This study demonstrates that early switch to a dexamethasone implant in patients with refractory DME results in superior visual outcomes compared with late switch, despite similar anatomical improvements. These findings underscore the importance of early intervention to prevent permanent retinal damage.

Treatment decisions should be individualized based on clinical characteristics, OCT findings, and risk of complications. Larger-scale prospective studies are needed to provide clearer guidance regarding the optimal timing of switching. Furthermore, comparative studies evaluating newer agents such as faricimab and brolucizumab are warranted to expand therapeutic options for refractory DME.

Disclosures

Ethics Committee Approval: This study was approved by The Ethics Committe of Prof. Dr. Cemil Tascioglu City Hospital (date: 07.11.23, approval code: E-48670771-514.99-228766276).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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Authorship Contributions:

Concept: G.K., D.Y.; Design: A.C., G.K.; Supervision: G.K., A.M.O.; Resource: A.C., T.U.; Materials: A.M.O., T.U.; Data Collection and/or Processing: O.A., T.U.; Analysis and/or Interpretation: A.M.O., O.A.; Literature Search: D.Y., O.A.; Writing: D.Y.; Critical Reviews: A.C., G.K.

Peer-review: Externally peer-reviewed.

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Original Article

Efficacy and Safety of Intravitreal Triamcinolone Acetonide Alone or Combined with Intravitreal Bevacizumab in the Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion

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Abstract

Objectives: To compare the efficacy and safety of intravitreal triamcinolone acetonide (IVTA) monotherapy versus combined intravitreal triamcinolone acetonide and bevacizumab (IVTA+IVB) therapy in the treatment of macular edema secondary to branch retinal vein occlusion (BRVO).

Methods: In this retrospective study, 66 eyes of 65 patients with BRVO-related macular edema were evaluated. Patients were divided into two groups: IVTA monotherapy (n=37) and IVTA+IVB combination therapy (n=29). Central macular thickness (CMT), best-corrected visual acuity (BCVA), and intraocular pressure (IOP) were measured at baseline, week 1, and months 1, 3, and 6 after injection.

Results: Both groups demonstrated significant improvements in BCVA and reductions in CMT compared with baseline ($p<0.001$), with no statistically significant differences between the groups at any follow-up time point. IOP was significantly elevated in the IVTA group at several time points ($p<0.05$), while the combination group showed stable IOP levels. New-onset glaucoma developed in 8 patients in the IVTA group and only 1 patient in the combination group. No serious ocular complications occurred in either group.

Conclusion: Both treatment regimens provided comparable anatomical and visual improvements; however, combination therapy was associated with a more favorable safety profile. Although the use of IVTA has declined in contemporary clinical practice in favor of intravitreal dexamethasone implants, this study suggests that IVTA alone or in combination may still offer a viable and cost-effective alternative in regions where access to current therapies is limited or in low-resource settings.

Keywords: Bevacizumab, branch retinal vein occlusion, cost-effective therapy, macular edema, triamcinolone acetonide

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Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy and can lead to significant visual impairment (1). RVO is classified into central RVO (CRVO) and branch RVO (BRVO). In BRVO, the primary cause of vision loss is macular edema, which typically results from the breakdown of the inner blood-retinal barrier, leading to fluid leakage from the vessels into the retinal tissue (1). This edema develops due to hypoxia and may cause irreversible structural damage to the macula if prolonged. Although macular edema in BRVO often resolves spontaneously within 6 to 12 months, therapeutic intervention is frequently required (2).

Grid laser photocoagulation was historically considered the standard treatment for macular edema secondary to BRVO based on the results of the Branch Vein Occlusion Study (BVOS), which demonstrated visual benefit compared with observation (3,4). As an alternative, intravitreal triamcinolone acetonide (IVTA) has been found to be effective in reducing edema and improving visual acuity. The SCORE-BRVO trial further evaluated intravitreal triamcinolone and demonstrated anatomical improvement, although with a higher incidence of intraocular pressure elevation compared with standard care (5). Corticosteroids exert anti-inflammatory and anti-angiogenic effects, reducing retinal vascular permeability.

In recent years, a better understanding of the role of vascular endothelial growth factor (VEGF) in the pathogenesis of edema and neovascularization has led to the widespread use of anti-VEGF agents such as bevacizumab (6). Large randomized controlled trials, including the BRAVO study, demonstrated that anti-VEGF therapy significantly improves visual acuity and reduces central macular thickness in BRVO (7). In addition, the GENEVA trial demonstrated that dexamethasone intravitreal implants provide significant anatomical and functional improvement in RVO-related macular edema, supporting the role of corticosteroids in selected cases (8). This study aimed to compare the efficacy and safety of IVTA monotherapy versus combination therapy with IVTA and IVB in the treatment of macular edema secondary to BRVO.

Methods

This retrospective study was conducted by reviewing the medical records of patients treated with intravitreal injections for macular edema secondary to BRVO between September 2006 and February 2009 at Ophthalmology Clinics 1 and 3 of the University of Health Sciences, Beyoglu Eye Training and Research Hospital. The diagnosis was confirmed by fundus examination, optical coherence tomography (OCT), and fundus fluorescein angiography (FFA).

A total of 66 eyes from 65 patients were included in the study. Patients were divided into two groups: the IVTA monotherapy group (n=37) and the combination therapy group receiving IVTA plus intravitreal bevacizumab (IVB) (n=29). Inclusion criteria were central macular thickness (CMT)>250 µm on OCT and absence of neovascularization or ischemia on FFA. Exclusion criteria included active neovascularization, other retinal diseases, and uncontrolled systemic illnesses. The Ethics Committee of Haseki Training and Research Hospital approved the study with the number 25-2025. Informed consent was waived due to the retrospective nature of the study.

All injections were performed under sterile operating room conditions using a standard technique. In phakic eyes, injections were administered 3.5 mm posterior to the limbus, and in pseudophakic eyes, 3.0 mm posterior to the limbus, from the inferotemporal quadrant. The IVTA group received 0.1 mL (4 mg) of triamcinolone acetonide (Kenacort-A 40; Deva Holding A.Ş., İstanbul, Türkiye), while the combination group received 0.05 mL (2 mg) of triamcinolone acetonide plus 0.05 mL (1.25 mg) of bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA). In the combination group, a half-dose of triamcinolone acetonide (2 mg) was used to minimize corticosteroid-related adverse effects while combining its anti-inflammatory activity with the anti-VEGF effect of bevacizumab. All patients received prophylactic antibiotic eye drops following the injection. Patients were evaluated before injection and at 1 week, 1 month, 3 months, and 6 months after injection. The assessments included best-corrected visual acuity (BCVA) using a Snellen chart, CMT measured by OCT, and intraocular pressure measured by Goldmann applanation tonometry. All OCT scans were obtained using Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA).

All analyses were performed using IBM SPSS Statistics for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Between-group comparisons were conducted using the independent-samples t-test for parametric data and the Mann–Whitney U test for non-parametric data. Within-group repeated measurements were evaluated using the paired-samples t-test for parametric data and the Wilcoxon signed-rank test for non-parametric data. Categorical variables, including complication rates, were compared using the chi-square test. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 66 eyes from 65 patients were included in the study. Of these, 37 eyes received IVTA monotherapy, while 29 eyes received a combination of IVTA and intravitreal bevacizumab (IVB). There were no statistically significant differ-

ences between the groups in terms of age, sex, systemic diseases, laterality of the affected eye, or the location of BRVO (Table 1). The mean follow-up duration was 12.1±8.3 months, and all analyses were conducted using data up to month 6.

At baseline, there were no significant differences between the groups in BCVA, CMT, or intraocular pressure (IOP) (Table 2). The mean baseline CMT was 475.8±113.3 µm in the IVTA group and 477.0±167.6 µm in the combination group. In both groups, CMT decreased significantly at all follow-up points (week 1 and months 1, 3, and 6) compared with baseline (p<0.001). In the IVTA group, CMT decreased from 475.8±113.3 µm at baseline to 298.0±90.2 µm at week 1 and 256.1±83.6 µm at month 1; although a partial increase was observed thereafter, CMT remained below baseline at month 3 and month 6 (334.6±137.5 µm and 343.5±167.6 µm, respectively). Similarly, in the combination group, CMT decreased from 477.0±167.6 µm at baseline to 290.1±147.6 µm at week 1 and 252.7±86.2 µm at month 1; despite a subsequent partial increase, CMT remained below baseline at month 3 and month 6 (274.5±146.8 µm and 328.2±132.5 µm, respectively). No statistically significant differences were found between the groups at any time point (Fig. 1).

Table 1. Demographic characteristics of the patients included in the study

	IVTA Group (n=37)	Combination Group (n=28)	p
Age (years±SD)	63.1±8.4	60.5±8.7	0.236
Sex			
Female	14	12	0.799
Male	23	16	
Systemic Disease			0.357
None	6	10	
DM	4	2	
HT	18	9	
DM + HT	8	6	
Glaucoma	1	2	
Affected Eye			0.226
Right	15	17	
Left	22	11	
BRVO Localization			0.861
Inferotemporal	12	10	
Superotemporal	25	18	

DM: Diabetes mellitus; HT: Hypertension; BRVO: Branch retinal vein occlusion; SD: Standard deviation

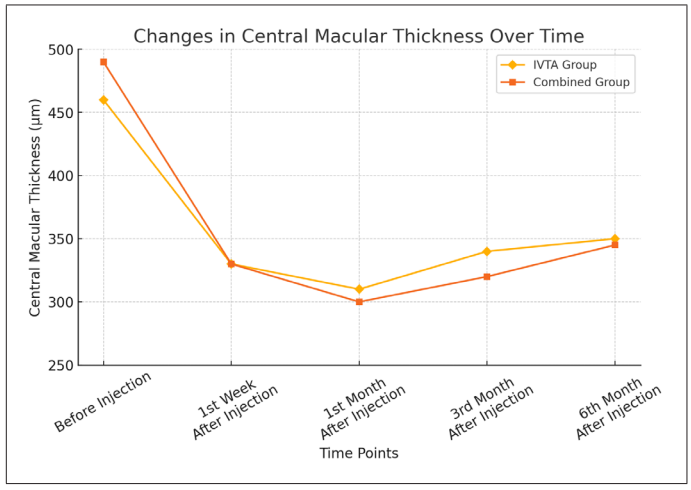

Figure 1. Change in Central Macular Thickness (CMT) Over Time in Both Treatment Groups. Mean CMT values (µm) are presented for each group at baseline and follow-up visits. Both the IVTA and combination groups showed significant reductions in CMT at all time points compared with baseline (p<0.001). No significant differences were observed between the groups at any visit. Error bars indicate standard deviation. Asterisks denote statistically significant differences compared with baseline (p<0.001).

Regarding BCVA, the IVTA group showed significant improvements at week 1 (median 0.10, p=0.015), month 1 (0.20, p=0.007), and month 3 (0.20, p=0.013), but not at month 6 (0.15, p=0.146) (Table 3). In the combination group, BCVA improvement was statistically significant at months 1 and 3 (both p<0.05), but not at week 1 or month 6. At all time points, there were no statistically significant differences in BCVA between the two groups (Fig. 2).

Regarding IOP, the baseline mean was 15.56±2.00 mmHg in the IVTA group and 15.31±3.10 mmHg in the combination group. In the IVTA group, a significant rise in IOP was observed at week 1 (17.00±2.94 mmHg, p=0.001), month 1 (17.45±3.27 mmHg, p<0.001), and month 3 (16.72±3.79

Table 2. Baseline comparison of clinical parameters between the IVTA and combination groups

Parameter	IVTA Group (n=37)	Combination Group (n=29)	p
Best-corrected visual acuity (Median [min–max])	0.10 (0–0.80)	0.10 (0.01–0.80)	0.467
Central macular thickness (µm) (Mean ± SD)	475.8±113.3	477.0±167.6	0.984
Intraocular pressure (mmHg) (Mean ± SD)	15.56±2.00	15.31±3.10	0.685

min: Minimum; max: Maximum; SD: Standard deviation; IOP: Intraocular pressure

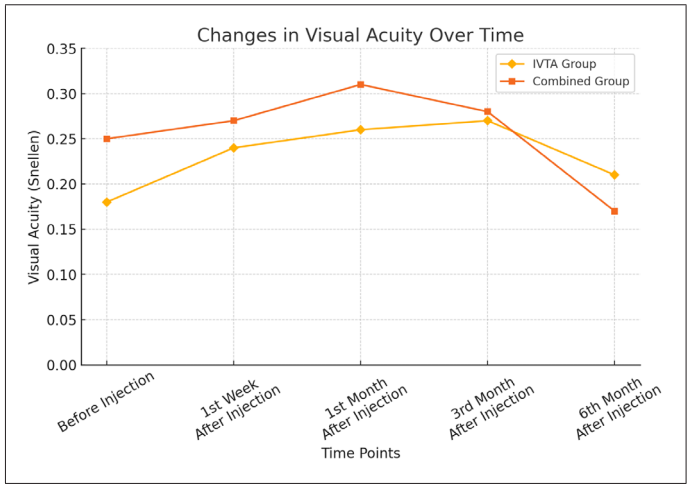

Figure 2. Change in Best-Corrected Visual Acuity (BCVA) Over Time in Both Treatment Groups. Median BCVA values (Snellen equivalents) at baseline, week 1, and months 1, 3, and 6 are shown. Significant improvements were observed in the IVTA group at week 1, month 1, and month 3 ($p<0.05$) and in the combination group at month 1 and month 3 ($p<0.05$). No statistically significant differences were found between the groups at any time point. Error bars represent the interquartile range. Asterisks indicate statistically significant differences compared with baseline ($p<0.05$).

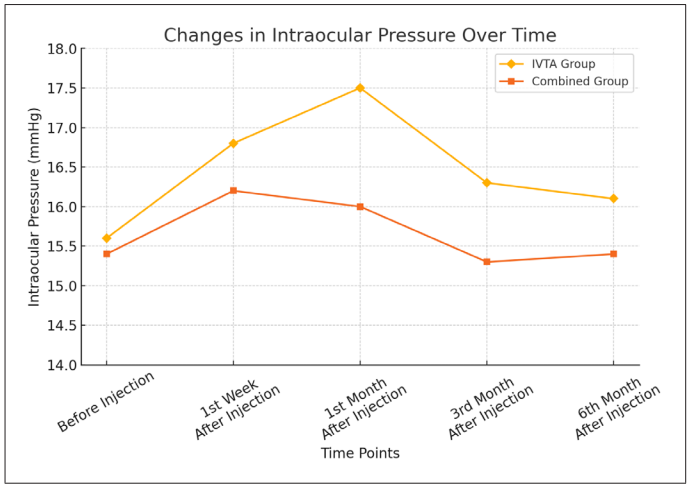

Figure 3. Change in Intraocular Pressure (IOP) Over Time in Both Treatment Groups. Mean IOP (mmHg) is displayed at baseline and during follow-up. The IVTA group exhibited significant increases in IOP at week 1, month 1, and month 3 ($p<0.05$). In the combination group, IOP changes were not statistically significant. A significant difference between the groups was observed only at month 1 ($p=0.044$). Error bars represent standard deviation. Asterisks indicate statistically significant changes compared with baseline ($p<0.05$).

mmHg, p=0.034), but not at month 6 (16.66±3.79 mmHg, p=0.128). In contrast, the combination group did not exhibit any statistically significant IOP changes throughout the follow-up period. Between-group comparisons revealed a significant difference only at month 1, when the IVTA group had higher IOP than the combination group (17.45±3.27 mmHg vs 16.00±2.13 mmHg, p=0.044); no other time points showed significant differences (Fig. 3).

Table 3. Visual acuity before and after injection in the IVTA group

Time Point	Median VA (min–max)	p
Pre-injection	0.10 (0–0.80)	–
1 week post-injection	0.10 (0.01–1.0)	0.015*
1 month post-injection	0.20 (0.01–1.0)	0.007†
3 months post-injection	0.20 (0.01–0.80)	0.013*
6 months post-injection	0.15 (0.01–0.80)	0.146

*VA: Visual Acuity (Snellen scale). Since the data were non-parametric, median and range (min–max) values were used. $p<0.05$, †$p<0.001$

No serious complications, such as endophthalmitis, retinal detachment, or traumatic cataract, were observed in either group. In addition to three patients with a known history of glaucoma, new-onset glaucoma developed in 8 patients in the IVTA group and 1 patient in the combination group. All were managed successfully with topical anti-glaucomatous treatment.

Discussion

In the present study, both IVTA and IVTA+IVB regimens produced significant anatomical and functional improvement in BRVO-related macular edema. However, IOP elevation and new-onset glaucoma were observed more frequently in the IVTA group, suggesting that combination therapy may provide comparable efficacy with a more favorable safety profile. These findings are partially consistent with the results of the SCORE-BRVO study, which demonstrated that intravitreal triamcinolone provides anatomical benefit in BRVO, although at the expense of higher rates of intraocular pressure elevation (5). Our results similarly showed a higher incidence of IOP elevation in the IVTA monotherapy group.

Given the central role of VEGF and inflammatory mediators in BRVO-related macular edema, intravitreal therapies have become the first-line approach. Intravitreal corticosteroids, particularly triamcinolone acetonide (IVTA), reduce edema through their anti-inflammatory, VEGF-suppressive, and blood-retinal barrier-stabilizing effects (9). In contrast, anti-VEGF agents such as bevacizumab (IVB) target all isoforms of VEGF, leading to rapid and effective resolution of edema (10). The combined use of these two pharmacologic classes, acting via different mechanisms, has recently garnered interest as a potentially synergistic strategy.

In our study, both IVTA and IVTA+IVB combination therapy resulted in significant improvements in BCVA and CMT. However, the rate of IOP elevation and new-onset glaucoma was significantly higher in the IVTA monothera-

py group, suggesting that combination therapy may offer a more favorable safety profile while achieving similar therapeutic outcomes.

In BRVO, the BRAVO trial established anti-VEGF therapy as the current first-line treatment, demonstrating rapid and significant visual improvement (7). Several randomized controlled trials have demonstrated that the functional and anatomical effects of a single intravitreal anti-VEGF injection in retinal vein occlusion are transient. In BRVO, large randomized clinical trials have consistently demonstrated that anti-VEGF therapy produces rapid and significant improvements in both best-corrected visual acuity (BCVA) and central macular thickness. In the BRAVO study, ranibizumab achieved a mean visual gain of approximately 16–18 letters at 6 months; however, sustained benefit required continued treatment during follow-up (7). Similar findings were reported in the VIBRANT study, in which aflibercept provided superior anatomical and functional outcomes compared with grid laser, with maintenance of visual gains dependent on ongoing intravitreal therapy (11). These results underscore the need for repeated injections to maintain disease control in BRVO-associated macular edema and indicate that the therapeutic durability of anti-VEGF agents in vein occlusion is limited.

The most common complication of IVTA is increased IOP, which typically develops within the first few weeks after injection (5). In our study, new-onset glaucoma was observed in 8 patients in the IVTA group and only 1 patient in the combination group, all of whom were successfully managed with topical medication. This supports the hypothesis that the reduced steroid dose in the combination group may mitigate IOP-related adverse effects. Similarly, the GENEVA trial demonstrated that dexamethasone implants are effective in RVO-related macular edema but are also associated with steroid-related adverse events, particularly IOP elevation and cataract progression (8). These findings further support the need to balance efficacy and safety when selecting corticosteroid-based therapies.

Corticosteroids may counteract this mechanism by directly suppressing VEGF expression. On the other hand, Turkseven Kumral et al. reported that ranibizumab treatment provided similar anatomical and functional improvements in macular edema secondary to both superior and inferior temporal BRVO; however, a higher number of injections was required to achieve the same efficacy in superior temporal BRVO cases (2). In our study, no recurrence of edema was observed in the combination group, indicating potentially longer-lasting efficacy.

None of the patients in our study developed serious injection-related complications, such as endophthalmitis. All procedures were performed under strict aseptic conditions, which likely contributed to the absence of adverse events and emphasized the importance of technique and patient selection alongside pharmacologic considerations.

Although previous studies have explored IVTA+IVB combination therapy, most of these studies are outdated and do not reflect current clinical practice, in which anti-VEGF monotherapy is preferred. IVTA is now used primarily in selected cases in which anti-VEGF monotherapy yields suboptimal results, frequent recurrence occurs, or systemic contraindications exist. Our study revisits the potential role of IVTA+IVB combination therapy, particularly with detailed monitoring of safety parameters such as IOP and glaucoma incidence. Comparable findings have recently been reported in prospective comparative studies, which demonstrated that IVTA provided longer-lasting anatomical improvement, while IVB yielded faster but less durable functional outcomes (5,12). Meanwhile, in a recent study, dexamethasone implants provided superior short-term anatomical and functional outcomes compared with continued anti-VEGF therapy in patients with BRVO-related resistant macular edema, although this benefit diminished over time (13,14). Although the current trend favors dexamethasone implants and anti-VEGF agents, recent evidence shows that IVTA still has a therapeutic role in selected clinical scenarios, such as bilateral diffuse uveal melanocytic proliferation, especially where cost considerations or access to implants are limiting factors (9).

Furthermore, recent prospective data have confirmed that intravitreal triamcinolone remains effective even after anti-VEGF failure, showing sustained reduction in CMT with comparable safety profiles between 2 mg and 4 mg doses in diabetic macular edema (15). Additionally, corticosteroid-related retinal toxicity has been discussed in recent preclinical studies. Schlichtenbrede et al. demonstrated in a mouse model that triamcinolone could induce structural toxicity at the retinal cellular level (16). This raises concerns that go beyond IOP and cataract formation and suggests that combination therapy, by reducing the steroid dosage, may minimize this risk.

Our findings demonstrate that both treatment strategies are effective in reducing macular edema and improving vision. However, IVTA monotherapy was associated with a significantly higher risk of IOP elevation and glaucoma. Combination therapy achieved similar functional and anatomical outcomes with fewer adverse effects. Combination therapy may theoretically reduce steroid exposure while maintaining therapeutic efficacy through complementary mechanisms of action targeting both VEGF-mediated and inflammatory pathways.

Given these findings, IVTA+IVB combination therapy may be considered a suitable option for patients at risk of steroid-induced IOP elevation. Nevertheless, larger, prospective, multicenter trials with longer follow-up and biomark-

er-based evaluations are necessary to validate these results and better define the pharmacodynamic synergy of combination therapy.

Limitations

This study has several limitations. First, its retrospective design may introduce selection bias and limit the ability to establish causal relationships. Second, although patients were clinically followed for up to one year, statistical analyses were restricted to data available through the 6-month visit, which may underestimate late-onset complications such as cataract progression. Our findings are in line with recent systematic reviews indicating that corticosteroid-associated cataract progression is generally mild within the first 6 months and rarely necessitates surgery (17). Third, the sample size was relatively small, and the results represent a single-center experience. Therefore, prospective multicenter studies with longer follow-up and larger cohorts are warranted to validate our findings.

Fourth, due to the retrospective design and the historical nature of the dataset, certain baseline variables, specifically the exact duration of BRVO symptoms before presentation and detailed documentation of lens status distribution, were not consistently recorded in all patient files and therefore could not be reliably extracted. Regarding systemic diseases, patients with uncontrolled systemic illnesses were excluded according to the study protocol; however, detailed subgroup distributions of controlled systemic conditions (e.g., hypertension, diabetes mellitus, hyperlipidemia) were not uniformly documented in a standardized manner at the time of data collection. Consequently, these parameters could not be included in the present analysis.

Conclusion

Although the combined use of IVTA and IVB was found to be as effective as IVTA monotherapy in improving both anatomical and functional outcomes, it was associated with significantly fewer IOP-related complications. This suggests that combination therapy may offer a safer alternative in selected cases. However, it should be noted that, in current clinical practice, the use of IVTA has significantly declined and is no longer considered a first-line treatment due to its side-effect profile and the widespread adoption of anti-VEGF monotherapy. Therefore, while our findings provide insight into the potential benefits of combination therapy, their relevance today lies primarily in specific clinical scenarios, particularly in settings where current long-acting corticosteroid implant therapies, such as dexamethasone or fluocinolone acetonide, are not available. Especially in low-income countries or among patients with limited financial resources, where access to newer or more expensive treatments may be restricted, IVTA-based regimens may still represent a viable and cost-effective alternative.

Disclosures

Ethics Committee Approval: This study was approved by The Ethics Committee of Haseki Training and Research Hospital (25-2025 – 05.03.2025).

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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Original Article

AI-Based Visual Prognosis in Full-Thickness Macular Hole Surgery Using the ILM Flap Technique

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Abstract

Objectives: This study evaluated the clinical utility of a multimodal large language model-based artificial intelligence (AI) model in predicting postoperative visual outcomes following full-thickness macular hole (FTMH) surgery using the inverted internal limiting membrane (ILM) flap technique.

Methods: A retrospective analysis was conducted on 45 patients who underwent pars plana vitrectomy for FTMH at a tertiary eye care center between January 2021 and December 2023. Preoperative optical coherence tomography (OCT) images, demographic data, and clinical parameters were analyzed using the AI model to predict best-corrected visual acuity (BCVA) at four postoperative time points. The predicted BCVA values were then compared with actual clinical outcomes.

Results: Preoperatively, the mean AI-predicted BCVA was 1.13±0.20 logMAR compared with the actual value of 1.24±0.33 logMAR (p=0.192). At 6 months, the predicted BCVA was 0.65±0.20 logMAR versus the actual value of 0.67±0.25 logMAR (p=0.528), and at 12 months, it was 0.47±0.17 logMAR versus 0.55±0.27 logMAR (p=0.155). However, at 7 days postoperatively, the model significantly overestimated visual impairment, predicting 1.37±0.28 logMAR versus the actual value of 1.07±0.33 logMAR (p<0.001). Spearman correlation analysis showed the strongest association between AI-predicted and actual BCVA at 6 months (r_s=0.5885, p<0.001), with a moderate correlation at 12 months (r_s=0.4156, p=0.005), a weak correlation preoperatively (r_s=0.3029, p=0.043), and no significant correlation at 7 days (r_s=0.1949, p=0.199).

Conclusion: These findings demonstrate the model's potential as a supportive tool for visual outcome prediction after FTMH surgery. The AI platform showed clinically relevant predictive performance for preoperative and later postoperative visual outcomes after FTMH surgery, particularly at 6 and 12 months, but was less reliable in the early postoperative period.

Keywords: Artificial intelligence, deep learning model, full-thickness macular hole, internal limiting membrane flap, multimodal large language model, visual prognosis

Introduction

Full-thickness macular hole (FTMH) is a sight-threatening retinal condition characterized by a full-thickness defect in the foveal region, leading to central vision loss (1). Its prevalence ranges from approximately 0.02% to 0.5% in populations over the age of 55 years, with a two- to three-fold higher incidence in women (2-4). Over the past decade, surgical advancements, particularly the introduction of the inverted internal limiting membrane (ILM) flap technique, have significantly improved both anatomical closure rates and functional

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visual outcomes, especially in large or chronic cases (5-7). Nevertheless, despite these technical improvements, accurately predicting postoperative best-corrected visual acuity (BCVA) remains a clinical challenge due to the multifactorial nature of visual recovery. Factors such as macular hole size, chronicity, and photoreceptor integrity contribute to the variability in outcomes, thereby complicating preoperative counseling and individualized surgical planning (5-7).

In routine clinical practice, providing patients with realistic expectations regarding visual improvement following surgery remains challenging. Because of this uncertainty, surgeons often adopt a cautious approach, emphasizing that the primary surgical objective is to preserve existing vision rather than to guarantee significant improvement. This cautious communication arises from the lack of reliable, evidence-based tools for forecasting visual outcomes. The idea for this study arose from this clinical dilemma: The need for a method that can estimate, with reasonable accuracy, the range of visual acuity a patient may achieve postoperatively.

In recent years, researchers worldwide have investigated the integration of artificial intelligence (AI) into clinical medicine. Ophthalmology is particularly well suited for advanced AI implementation due to its extensive reliance on digital imaging techniques. At present, AI systems have been developed to interpret various ophthalmic images, including fundus photographs, optical coherence tomography (OCT) scans, and visual field tests. These systems are trained using large datasets of medical images and are subsequently validated using separate datasets to ensure accuracy. AI has demonstrated the ability to reliably detect several eye diseases, such as diabetic retinopathy, glaucoma, cystoid macular edema, and age-related macular degeneration. Given that the diagnosis and treatment of macular hole (MH) are largely dependent on imaging, this condition stands to benefit significantly from AI advancements (8-12). In addition to image interpretation, research has also focused on employing AI to forecast visual outcomes using regression models based on clinical parameters. In cases of MH, features such as hole size, BCVA, and duration of symptoms have been used as input variables for these predictive models.

Large language models (LLMs) have recently emerged as a transformative tool in ophthalmic AI. Systems such as ChatGPT, which leverage advanced LLM architectures, are capable of synthesizing diverse information sources to support clinical decision-making, including surgical planning and disease education (13-15). Unlike traditional machine learning (ML) models, which rely heavily on structured datasets, LLM-based multimodal AI systems are designed to process and contextualize heterogeneous data types, including images, clinical records, and narrative texts, thereby enhancing their flexibility and applicability in real-world clinical environments. Therefore, this study aimed to determine whether an LLM-based tool could generate clinically meaningful BCVA estimates after inverted ILM flap surgery for MH.

Methods

Study Settings

This retrospective study was conducted at a tertiary eye care center following approval by the local ethics committee (No. 4-2025). All research procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Due to the non-interventional, retrospective nature of the study and the absence of identifiable patient data, the requirement for informed consent was formally waived by the institutional review board.

Medical records of patients who underwent pars plana vitrectomy (PPV) using the inverted ILM flap technique were reviewed. The analysis included cases performed between January 2021 and December 2023. All eligible consecutive cases that met the predefined criteria at the selected study time points were included; therefore, no a priori sample size calculation was performed.

The inclusion criteria consisted of patients who had undergone a comprehensive ophthalmologic evaluation before surgery, had a MH size greater than 200 μm, and had complete follow-up data available preoperatively and at postoperative day 7, 6 months, and 12 months.

The exclusion criteria included the presence of any ocular condition that could potentially affect visual recovery, such as diabetic retinopathy, high myopia (spherical equivalent of ≥−6.00 diopters), glaucoma, uveitis, age-related macular degeneration, and poor-quality OCT images.

Demographic and clinical data were collected, including age, sex, MH size, closure status, and BCVA at the specified time points. BCVA measurements were converted to the logarithm of the minimum angle of resolution (logMAR) for standardized analysis.

Surgical Procedure

All patients underwent 25-gauge PPV, followed by ILM staining using 0.15% trypan blue ophthalmic solution (Membrane Blue, DORC, the Netherlands). The stained ILM was carefully grasped using Grieshaber 25GA forceps (Alcon), and the inverted ILM flap technique was performed. The surgery concluded with fluid-air exchange, and all patients were instructed to maintain a prone position for 3 days postoperatively. All patients received a combination of antibacterial and anti-inflammatory eye drops (Dexamethasone and Tobramycin) for 1 month following surgery.

AI-Based Visual Acuity Prediction

OCT Master, a customized implementation of OpenAI's ChatGPT architecture integrated into the MatrixEye platform,

was used to analyze OCT images and predict postoperative visual outcomes. For each case, the platform received the following preoperative inputs: Preoperative OCT images, patient age, duration of visual deterioration, and minimum linear diameter of the MH. The uploaded image included 3 principal components: An infrared fundus image centered on the macula, a horizontal OCT B-scan passing through the full-thickness macular hole, and the corresponding ETDRS-based retinal thickness map. An example of the uploaded OCT image is shown in Figure 1. In addition to the image, the following clinical variables were entered using a standardized text prompt: Patient age, duration of visual symptoms, and minimum linear diameter of the macular hole. No additional clinical variables, such as baseline BCVA, biometry data, or postoperative OCT images, were provided.

Based on these inputs, the platform was instructed to calculate the probability of successful anatomical closure of the MH and generate a range of BCVA values, including both minimal and maximal predictions, at 4 time points: Preoperatively and at postoperative day 7, month 6, and month 12. Mean predicted BCVA was calculated using the following formula: Mean predicted BCVA=(Minimal predicted BCVA + Maximal predicted BCVA)/2. Subsequently, the AI-generated outputs were compared with actual clinical BCVA measurements at the corresponding postoperative intervals. The AI model was used as a commercially available out-of-the-box platform and was not additionally trained, tuned, or modified by the study investigators. Therefore, the present report describes the input-output workflow used in clinical testing, whereas the internal architecture and training process of the proprietary model were not accessible to the authors. A schematic diagram of the AI workflow and data inputs is shown in Figure 2.

Prompt example: The patient is __ years old and has a macular hole with a minimum linear diameter of __ microns. Visual symptoms have been present for __ months. Based on the input data and OCT image: (i) Predict preoperative BCVA; (ii) predict postoperative BCVA prognosis at 7 days, 6 months, and 12 months; and (iii) estimate the probability of macular hole closure after surgery.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 10 software (GraphPad Software Inc., San Diego, CA, USA). Continuous variables are presented as mean±standard deviation (SD). Agreement between mean predicted BCVA and actual BCVA at each time point was assessed using the nonparametric Wilcoxon signed-rank test. Patient-level associations between AI-predicted and actual BCVA values were evaluated using Spearman rank correlation analysis, and correlation coefficients were reported with 95% confidence intervals (CIs). For subgroup analyses comparing eyes with successful and failed anatomical closure, continuous variables were compared using the Mann–Whitney U test. Exploratory univariable logistic regression analysis was performed

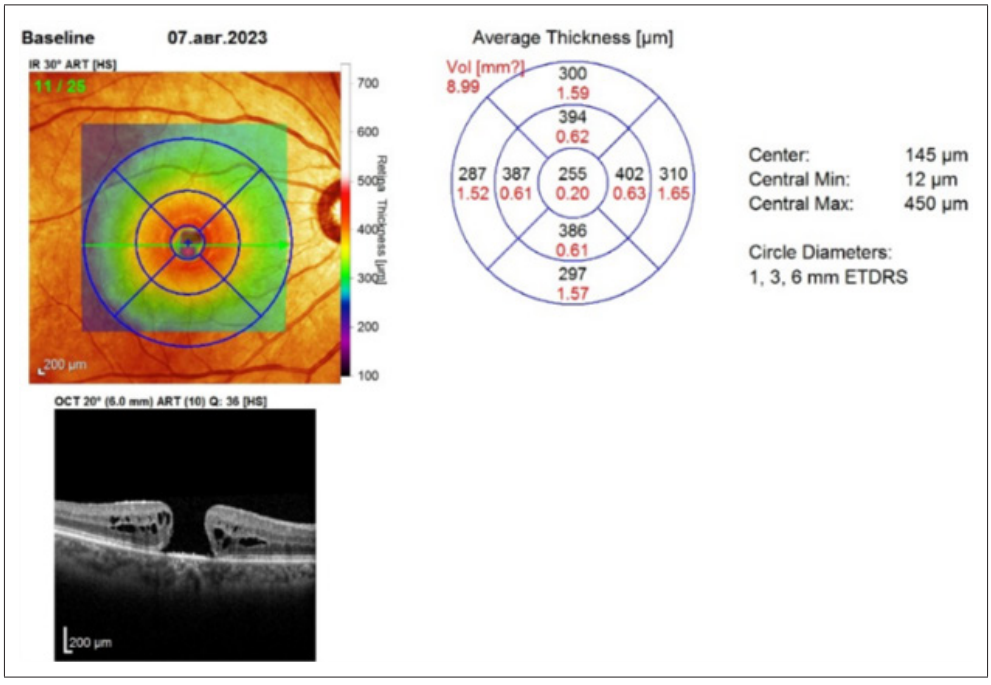

Figure 1. Example of a preoperative OCT image uploaded to the AI platform for visual outcome prediction. The image includes an infrared fundus view centered on the macula, a horizontal OCT B-scan demonstrating the full-thickness macular hole, and the corresponding ETDRS retinal thickness map.

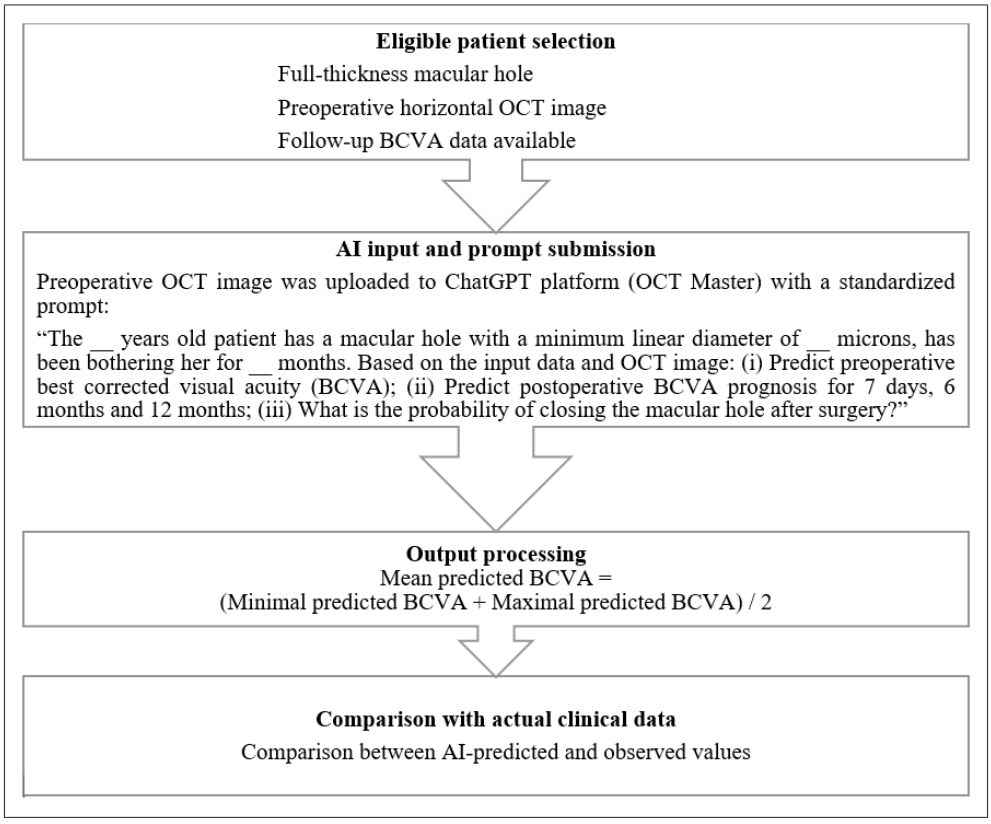

Figure 2. Schematic diagram of AI workflow and data inputs.

to identify preoperative factors associated with anatomical non-closure. The results of logistic regression are presented as odds ratios (ORs) with 95% CIs. All p-values were two-tailed, and $p<0.05$ was considered statistically significant.

An approximate post hoc power analysis was performed for the observed correlations between AI-predicted and actual BCVA values using Fisher's z transformation of the correlation coefficients, assuming a two-sided α level of 0.05. Because the study was retrospective, these power estimates were considered supportive rather than primary.

Results

A total of 45 patients who underwent FTMH closure using the inverted ILM flap technique were included in the analysis. The mean age of the cohort was 68.64±6.71 years. The anatomical closure rate was 86.7%, with 6 cases (13.3%) remaining unclosed. Among these, 1 case (2.2%) demonstrated flap detachment. The average MH diameter was 523.1 μm, with a range of 280 to 1200 μm.

Table 1 shows a comparison between AI-predicted and actual BCVA values across 4 time points. Preoperatively, the mean predicted BCVA (1.13±0.20 logMAR) closely approx-

Table 1. Comparison of AI-Predicted and Actual Best-Corrected Visual Acuity (BCVA) in the logarithm of the minimum angle of resolution (logMAR) at Preoperative and Postoperative Time Points

Timepoint	Minimal predicted BCVA (logMAR)	Maximal predicted BCVA (logMAR)	Mean predicted BCVA (logMAR)	Actual BCVA (logMAR)	p[1]
Preoperatively	1.31±0.26	0.96±0.16	1.13±0.20	1.24±0.33	0.192
7 days postoperatively	1.57±0.33	1.16±0.23	1.37±0.28	1.07±0.33	<0.001*
6 months postoperatively	0.75±0.23	0.54±0.18	0.65±0.20	0.67±0.25	0.528
12 months postoperatively	0.57±0.21	0.38±0.15	0.47±0.17	0.55±0.27	0.155

[1]Nonparametric Wilcoxon signed-rank test was used to compare Mean predicted BCVA with Actual BCVA; *statistically significant; BCVA: Best-Corrected Visual Acuity; logMAR: logarithm of the Minimum Angle of Resolution.

imated the actual value (1.24±0.33 logMAR), with no statistically significant difference (p=0.192). At 7 days postoperatively, the tool significantly overestimated visual impairment, with a mean predicted BCVA of 1.37±0.28 logMAR and an actual BCVA of 1.07±0.33 logMAR (p<0.001). By 6 months, the mean predicted BCVA (0.65±0.20 logMAR) was nearly identical to the actual measurement (0.67±0.25 logMAR), with no significant difference (p=0.528). At 12 months postoperatively, the predicted value (0.47±0.17 logMAR) remained close to the actual BCVA (0.55±0.27 logMAR), again showing no statistically significant difference (p=0.155).

Correlation Between AI-Predicted and Actual BCVA Values

To further evaluate patient-level agreement, Spearman rank correlation analysis was performed between AI-predicted and actual BCVA values at each study time point (Fig. 3). Preoperatively, a weak but statistically significant positive correlation was observed between predicted and actual BCVA (r =0.3029, 95% CI 0.0014 to 0.5540, p=0.043). At 7 days postoperatively, the correlation was weak and not statistically significant (r =0.1949, 95% CI −0.1134 to 0.4690, p=0.199).

In contrast, the model showed a moderate positive correlation at 6 months, which was the strongest association among all assessed time points (r =0.5885, 95% CI 0.3488 to 0.7560, p<0.001). At 12 months postoperatively, the correlation remained moderate and statistically significant (r =0.4156, 95% CI 0.1303 to 0.6374, p=0.005).

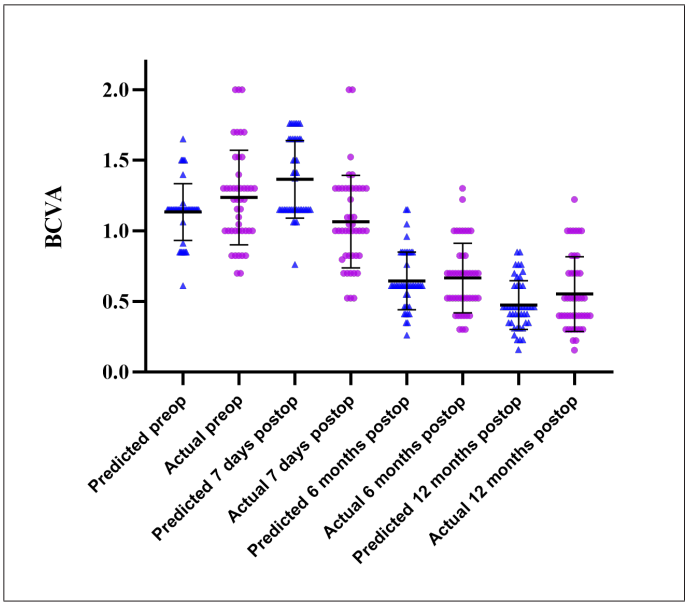

Figure 3. Distribution of AI-predicted and actual BCVA values at the preoperative stage and at 7 days, 6 months, and 12 months after surgery. Blue triangles represent AI-predicted values, and purple circles represent actual clinical measurements. Horizontal bars indicate mean values with SD.

Comparison Between Successful and Failed Surgery Subgroups

A subgroup analysis was performed comparing eyes with successful anatomical closure (n=39) and those without closure (n=6). The overall anatomical closure rate was 86.67%. Eyes in the failed-surgery subgroup tended to have a larger minimum linear diameter of the macular hole (613.33±231.06 μm) than eyes with successful closure (509.21±176.53 μm), although this difference did not reach statistical significance (p=0.292). Likewise, the AI-predicted probability of closure was lower in the failed subgroup (85.83±9.70%) than in the successful subgroup (90.28±4.87%, p=0.315).

Univariable analysis was performed to identify preoperative factors associated with anatomical non-closure. Axial length did not differ between the successful and failed-surgery groups (23.50±0.84 mm vs. 23.52±1.02 mm, p=0.894) and was not associated with the risk of non-closure (OR per 1-mm increase, 1.03; 95% CI 0.38–2.84; p=0.951). No statistically significant predictors of non-closure were identified. However, a larger minimum linear diameter of the macular hole (OR per 100 μm, 1.30; 95% CI 0.86–1.97; p=0.215) and a lower AI-predicted probability of closure (OR per 1% increase, 0.89; 95% CI 0.78–1.02; p=0.100) showed non-significant trends toward association with failed anatomical closure.

Post-hoc Power Analysis

Based on the observed correlation coefficients between AI-predicted and actual BCVA values and assuming a two-sided α of 0.05, the approximate achieved power at the current sample size (n=45) was 99.2% at 6 months and 81.8% at 12 months.

Discussion

The findings of our study show that the AI model is capable of generating clinically relevant predictions of postoperative visual acuity after FTMH surgery. The predicted BCVA closely approximated actual clinical outcomes at the preoperative stage, as well as at 6 and 12 months postoperatively, using only raw preoperative OCT images and a limited set of clinical variables.

However, a significant deviation was observed at 7 days after surgery, when the model systematically overestimated visual impairment. This may be partially attributed to the specific surgical technique used in this study, which involved fluid-air exchange rather than gas tamponade. Air tamponade may allow earlier functional recovery due to its shorter intraocular presence. Because the AI model was trained on generalized preoperative data and was not exposed to variations in postoperative tamponade strategies, its predictions may not fully capture the accelerated visual recovery associated with air-based approaches. Future refinement of

the model using stratified training data that reflect different surgical protocols could improve its short-term predictive accuracy.

At present, deep learning (DL)-based models represent the predominant form of AI in the field of medicine, as these models rely on more accurate numerical data and are considered to provide more reliable results (15-27). In the literature, we found a significant number of studies dedicated to the use of DL models in the analysis, prognosis, and treatment of macular holes (19-22).

A growing body of research has explored the application of AI to FTMH diagnosis and outcome prediction, with each study highlighting distinct strengths and limitations in model design, data input, and clinical utility (13). For instance, Pereira et al. demonstrated that a three-dimensional DL model could accurately segment macular hole volume on OCT scans, with a strong correlation with manual measurements (15). Their findings further revealed that volumetric analysis correlated more closely with postoperative visual improvement than conventional metrics.

Kim et al. employed a DL model trained on fundus photographs and reported 87.42% classification accuracy using the ResNet50 architecture (16). While their model successfully differentiated multiple retinal conditions, including macular holes, diabetic retinopathy, and retinal vein occlusion, reliance on fundus photography alone limited diagnostic precision for macular holes, suggesting the importance of OCT-based data in such cases.

Frawley et al. investigated a lightweight three-dimensional U-Net model that achieved segmentation performance comparable to that of more complex architectures while using fewer parameters and computational resources, making it practical for integration into clinical workflows (17). Similarly, the self-supervised RaSCL approach achieved perfect classification performance (F1=1.0) on OCT images of FTMH, even with a limited dataset, demonstrating the potential of contrastive learning for small-data medical imaging tasks.

The retrospective study by Lachance et al. analyzed data from 121 patients who underwent surgery for idiopathic FTMH (18). Only cases with anatomically confirmed macular hole closure at 6 months postoperatively, based on high-definition OCT B-scans, were included for model development. A hybrid predictive model was constructed by combining convolutional neural network (CNN)-derived outputs with clinical features. These results suggest that while DL offers complementary value, clinical variables, particularly baseline BCVA, remain the most influential predictors of postoperative visual improvement.

The study by Godbout et al. provides a critical perspective on the limitations of DL in small medical datasets, specifically for predicting visual improvement following macular hole surgery (19). Using a dataset of 121 patients, each with 2 high-resolution OCT scans and associated clinical data, the authors explored various deep vision models, including ResNet-50 with different pretraining strategies and lightweight CBR architectures, under a constrained data regime. Despite implementing multiple state-of-the-art training techniques, such as transfer learning, self-supervised pretraining, data augmentation, and model regularization, none of the DL models outperformed a simple logistic regression model trained solely on clinical features. Moreover, in a combined model in which CNN outputs were fused with clinical features, the CNN predictions contributed the least to decision-making, while baseline visual acuity dominated feature importance. The study highlights the importance of model selection based on data availability and cautions against overreliance on DL when the training dataset is not sufficiently large or diverse.

The study by Xiao et al. demonstrates the potential of ML models to predict short-term anatomical outcomes following MH surgery with high accuracy (20). Using preoperative OCT features and clinical variables from 288 eyes across 4 centers, the authors trained and validated 5 ML algorithms, with random forest achieving the best performance. Their findings support the feasibility of ML-based preoperative prediction tools to assist in personalized surgical planning and risk assessment for patients with IMH.

The multicenter study by Hu et al. provides compelling evidence for the utility of DL models in predicting postoperative MH status following vitrectomy and ILM peeling (21). By leveraging a large and diverse dataset across multiple clinical sites, the authors demonstrated that AI can achieve high predictive accuracy, thereby offering a potential tool for surgical planning and patient counseling. The model's ability to integrate complex imaging features and clinical parameters may facilitate the early identification of patients at risk for suboptimal anatomical outcomes, ultimately contributing to more personalized and evidence-based care. These findings highlight the growing role of AI in ophthalmic surgery and the need for further prospective validation and integration into clinical workflows.

Similarly, the study by Kucukgoz et al. presents a novel uncertainty-aware regression model that predicts postoperative visual acuity based on preoperative OCT images (22). Unlike standard models, U-ARM integrates uncertainty estimation, enabling clinicians to assess the reliability of predictions. The model demonstrated superior performance across internal, external, and out-of-sample datasets, achieving lower prediction errors and higher robustness compared with baseline approaches. Importantly, U-ARM effectively identified high-risk or anomalous cases through elevated uncertainty scores, providing a valuable safeguard in clinical

decision-making. This approach represents a significant step toward the deployment of trustworthy DL systems in ophthalmology.

In parallel, a study by Kwon et al. demonstrated the accuracy of a generative DL model in predicting postoperative macular anatomy from baseline OCT images (23). Their model was capable of reconstructing high-fidelity anatomical projections following MH surgery, thus adding anatomical insight to functional outcome prediction. Such approaches are highly relevant to surgical planning and could complement models aimed at forecasting visual recovery.

Recent advances underscore the growing role of multimodal imaging in improving prediction accuracy. Rizzo et al. emphasized the synergistic potential of combining OCT angiography (OCTA) and AI for the personalized management of macular holes (24). Their approach incorporated vascular biomarkers derived from OCTA images, particularly those related to the foveal avascular zone, into predictive frameworks. The integration of microvascular parameters, such as capillary density and perfusion index, was shown to enhance the granularity of disease characterization and prognosis estimation. These findings align with the direction of our research and suggest that supplementing structural OCT with OCTA-derived data could further increase the accuracy and relevance of AI-based prognostic models. Future progress in this field will likely depend on multimodal predictive systems that integrate structural OCT, OCTA-derived vascular biomarkers, and clinical metadata into a unified framework, which may improve prognostic accuracy and support more individualized surgical counseling.

All previously published AI studies on FTMH have reported quantitative performance metrics using conventional DL or ML frameworks. In contrast, our study evaluated a LLM-based platform that operates through natural-language interaction and does not require custom model training by the end user. The review by Jin et al. summarized 108 studies focused on the application of LLMs in ophthalmology: Automated question-answering (55 studies), information screening (27 studies), predictive modeling (11 studies), summarization (5 studies), diagnosis (5 studies), and image analysis (5 studies) (13,14,25-28). Among these reports, 32 focused specifically on retinal diseases. These works explored a broad range of LLM applications in managing prevalent retinal conditions, such as diabetic retinopathy, age-related macular degeneration, retinal vein occlusion, retinal artery occlusion, and central serous chorioretinopathy. They emphasized that ChatGPT can improve patient satisfaction by delivering accurate and well-formulated responses, particularly in the context of common retinal diseases. However, no prior studies specifically evaluated LLM-based individualized visual prognosis after FTMH surgery.

An important distinction between the present study and prior AI reports on FTMH surgery lies in the model paradigm and intended clinical use. Previous studies have generally relied on supervised DL or ML pipelines trained on curated OCT datasets, often combined with structured clinical variables, to predict a single predefined endpoint, such as visual improvement or postoperative visual acuity (13,14). For example, Lachance et al. developed a hybrid model combining a convolutional neural network-based model using preoperative HD-OCT B-scans with logistic regression using clinical features; notably, baseline visual acuity contributed more strongly to prediction than the OCT-based DL output itself (18). More recently, Kucukgoz et al. proposed an uncertainty-aware regression model trained on preoperative OCT images that generated numerical postoperative visual acuity predictions together with uncertainty estimates (22). In contrast, our study evaluated a proprietary multimodal LLM-based platform used in an out-of-the-box manner, without study-specific training or fine-tuning by the investigators, and queried through a standardized natural-language prompt rather than a conventional model-development workflow. The system accepted heterogeneous inputs, namely a representative preoperative OCT screenshot and selected clinical descriptors, and returned clinically interpretable outputs, including a prognostic BCVA range and estimated probability of hole closure. Therefore, the main contribution of the present study is not the development of another task-specific supervised model but the demonstration that a prompt-driven, clinician-facing multimodal AI tool may provide practically useful visual prognosis in a real-world retinal workflow.

A particularly noteworthy feature of the ChatGPT model is its ability to generate a prognostic range, defined by minimal and maximal predicted BCVA values (29). This approach takes into account the natural variability in surgical outcomes and provides a more informative tool for preoperative counseling. By presenting a range of possible visual acuity values rather than a single estimate, the model helps patients better understand what to expect after surgery, which may support more realistic expectations and shared decision-making.

The user-friendly design of the AI system, based on natural-language interaction, further enhances its clinical applicability. Unlike models that require technical expertise, segmentation, or code-based interfaces, the system accepts intuitive commands and outputs readable results (30). This simplifies its integration into clinical workflows and makes it accessible to a wider range of ophthalmologists. The system can be deployed with minimal infrastructure, requiring only access to digital OCT imaging and a secure connection to the AI platform (31).

In practice, such a platform may help surgeons internally structure prognosis estimation, define a plausible range of expected visual recovery, and prepare for more individualized preoperative counseling. At the same time, AI-generated estimates should not be interpreted as deterministic outcomes or communicated to patients without careful clinical contextualization. Because postoperative recovery may vary substantially, unmet expectations can undermine confidence in surgical care. Therefore, at the present stage of development, multimodal LLM-based tools should be viewed primarily as aids to physician judgment and counseling preparation rather than as independent sources of patient-directed prognostic advice.

Despite the promising results, several limitations should be acknowledged. First, the study was retrospective, single-center, and based on a relatively small sample. Although the internal consistency of the results supports the model's feasibility, external validation using larger, multi-institutional datasets will be necessary to confirm its generalizability across broader patient populations and varied surgical techniques. Because inclusion required adequate preoperative imaging and complete follow-up at the selected time points, selection bias cannot be excluded. Second, an important methodological consideration is that the AI model was not independently trained or customized by the study team. Instead, we used a pre-existing, commercially available AI platform into which we uploaded preoperative OCT images and clinical parameters. This approach has both strengths and weaknesses. On the one hand, it limits transparency regarding the model's internal architecture, training dataset composition, and learning process, which restricts full control over optimization and interpretability. On the other hand, it demonstrates the practical feasibility of using an out-of-the-box solution in a real-world clinical setting, without the need for technical development or model engineering. This makes the tool highly accessible and immediately applicable for clinicians who do not have experience in ML or programming, thereby supporting wider clinical adoption. Third, patient-level agreement analyses, external validation, and multimodal augmentation with OCTA were beyond the scope of the present pilot dataset. These issues should be addressed in future prospective multicenter studies.

A major concern regarding the use of LLMs for medical applications is the lack of reproducibility, as these generative models may not consistently provide the same answers, potentially affecting the reliability of their outputs in clinical settings. Addressing these challenges will be essential to fully realize the potential benefits of LLMs in ophthalmology and to ensure their responsible and ethical implementation in patient care.

Conclusion

This study demonstrates the feasibility and clinical relevance of using an LLM-based AI model to predict visual outcomes following FTMH surgery. Its ability to generate a prognostic range and operate through natural-language commands represents a substantial advancement in ophthalmic AI tools. With further optimization and validation, such systems have the potential to become integral components of personalized surgical planning and patient communication in retinal practice.

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Ethics Committee Approval: This study was approved by The Institutional Review Board, Expert Council of Kazakh Eye Research Institute, Almaty, Kazakhstan (№4-2025) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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Authorship Contributions:

Concept: L.O., E.K.; Design: L.O., K.R.; Supervision: L.O., E.K.; Resource: L.O., E.K.; Materials: L.O., A.K.; Data Collection and/or Processing: A.K., K.R., L.O.; Analysis and/or Interpretation: A.K., K.R., L.O.; Literature Search: A.K., K.R.; Writing: A.K., K.R., L.O.; Critical Reviews: L.O., K.R., A.K.

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Letter to Editor

Enhancing Müller Muscle-Conjunctival Resection: A Novel Cannula-Guided Technique

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The Müller muscle-conjunctival resection (MMCR) technique, initially introduced by Putterman and Urist in 1975, has gained popularity due to its rapid recovery time, absence of visible scarring, procedural simplicity, and relatively shallow learning curve (1). Traditionally, MMCR has been employed for the correction of minimal ptosis (2 mm or less). However, recent evidence suggests its applicability in cases of severe ptosis and as an adjunct to levator procedures for residual ptosis (2-5). In this letter, we aim to elucidate the application of a widely available 24-gauge cannula as a guide for the Putterman clamp. This technique facilitates surgical procedures without the need for additional assistance.

The surgical procedure was performed as follows: The upper eyelid was everted using a Desmarres retractor, and half of the preoperatively planned resection length was marked from the superior border of the tarsus to the upper fornix on the conjunctival surface at three points aligned with the pupil and the margins of the medial and lateral limbus. Two percent lidocaine with 1:100,000 epinephrine was injected subconjunctivally superior to the tarsal border of the upper eyelid. While awaiting the effect of the anesthetic, it was verified whether the Putterman clamp could be operated with one hand. A 24-gauge guide cannula was introduced through the temporal conjunctival marking, advanced posterior to the Müller muscle, passed through the central marking, and then directed toward the nasal marking. At the nasal marking, the tip of the cannula was brought out through the conjunctiva and secured with a mosquito clamp. While the cannula was pulled upward, the tarsus was drawn downward to widen the space, allowing the clamp to grasp the area more easily. Following entrapment of the conjunctiva and Müller muscle with the Putterman clamp, the guide cannula was removed, and local anesthetic solution was injected transcutaneously at the planned entry and exit sites of the sutures. A 6/0 polypropylene suture was introduced through the skin 1–2 mm below the skin crease and exited from the conjunctival side adjacent to the superior border of the tarsus medially. It was then passed in a running horizontal mattress pattern to the lateral end. The suture was passed through the full thickness of the eyelid and exited 1–2 mm below the skin crease. After insertion of a bolster, the suture was passed back through the skin adjacent to the temporal exit site and run in a reverse horizontal mattress pattern, passed through the full thickness of the eyelid near the first entry site, and tied over a bolster. A No. 11 Bard-Parker blade, angled with the sharp surface directed toward the clamp, was used to excise the entrapped tissue. The eyelid was inverted, antibiotic ointment was applied, and the eye was patched for 1 day.

Recent literature has documented the development of sutureless techniques that reduce operative complexity and

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assistant dependence while maintaining good outcomes (6-8). The cannula step described herein can also be incorporated into this technique. Recent modifications of MMCR techniques aim to simplify surgical steps. Kaynak et al. described the "PEANUTS" technique, which omits the Putterman clamp, potentially requiring greater surgical experience for adequate tissue control (9). In contrast, our technique incorporates cannula guidance while retaining the Putterman clamp, enhancing tissue stabilization and enabling a safer and more controlled incision.

This approach enables us to bypass the silk suture step traditionally required in MMCR surgeries. The use of a guide cannula enhanced our control of the conjunctiva and Müller muscle, thereby minimizing the need for assistance. Although operative time was not formally assessed, omission of the suturing step simplifies the procedure and is expected to shorten the surgical duration.

https://youtu.be/8_tkS32sjEE

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Case Report

Sinonasal Adenoid Cystic Carcinoma Presenting as a Retroorbital Mass: A Case Report

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Abstract

Although sinonasal adenoid cystic carcinoma (ACC) mainly originates from the salivary glands and lacrimal gland, approximately 10–25% of cases may arise from the sinonasal cavity and paranasal sinuses. Orbital involvement typically occurs due to local spread. Only a few cases of isolated orbital ACC without another primary focus have been documented. This report aims to describe a case of sinonasal ACC presenting as a retroorbital mass, raise awareness of this tumour and its rare presentation among both ophthalmologists and otolaryngologists, and provide brief information on its treatment. A 74-year-old female who presented to an external centre with progressive periorbital oedema, congestion, proptosis, and exotropia in her right eye for approximately 4 months was referred with a right retrobulbar mass. During the initial examination, the best-corrected visual acuity was 0.05 in the right eye (OD) and 0.8 in the left eye (OS). There was no significant pathology in the anterior or posterior segments. Eye movements were normal in the OS and moderately restricted in the OD, particularly in upgaze. She reported no otorhinolaryngological complaints, and her examination was normal except for a polyp-like lesion extending from the middle to the inferior meatus. Maxillofacial and orbital magnetic resonance imaging revealed a mostly homogeneous malignant soft tissue lesion extending from the retro-orbital area to the orbital apex, ethmoid cells, and nasal cavity. The patient underwent tumour excision via an inferior transconjunctival approach and endoscopic sinus surgery. Both nasal and intraorbital surgical excision specimens were consistent with ACC on histopathological examination.

Keywords: Adenoid cystic carcinoma, exotropia, histopathology, proptosis, retroorbital mass

Introduction

Adenoid cystic carcinoma (ACC) is a malignant neoplasm that usually originates from the major or minor salivary glands and, less frequently, from the lacrimal gland. It constitutes less than 1% of all head and neck malignancies and approximately 5% of paranasal sinus malignancies (1). It is slightly more common in women, with a mean age at diagnosis of 60 years (2). In ophthalmologic practice, ACC often presents as a superotemporal orbital mass originating from the lacrimal gland (3).

However, ACC can also arise from the paranasal sinuses, nasoapharynx, larynx, external auditory canal, trachea, breast, cervix, and skin (4). Tumours that originate from the paranasal sinuses and nasopharynx are referred to as sinonasal ACC. The maxillary sinus is the most common site for these tumours, followed by the nasal cavity and ethmoid and sphenoid sinuses (2). In a patient presenting with a sinonasal

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mass, pain, nasal obstruction, epistaxis, and auditory symptoms, sinonasal ACC should be considered in the differential diagnosis.

This report aims to describe a case of sinonasal ACC presenting as a retroorbital mass, raise awareness of this tumour and its rare presentation among both ophthalmologists and otolaryngologists, and provide brief information on its treatment.

Case Report

A 74-year-old female patient who presented to an external centre with progressive periorbital oedema, congestion, proptosis, and exotropia in her right eye for approximately 4 months was referred with a right retrobulbar mass. Her medical history included thyroidectomy, bladder prolapse repair, and cataract surgery, all performed more than 10 years earlier. She also had well-controlled diabetes mellitus and hypertension. No deterioration was observed in her current thyroid function tests. During the initial examination, the best-corrected visual acuity was 0.05 (from the superior half) in the right eye (OD) and 0.8 in the left eye (OS). Anterior segment examination revealed bilateral pseudophakia. Posterior segment examination revealed no significant findings except for a bilateral moderate increase in the disc-cup ratio (0.6 and 0.7 for OD and OS, respectively). Periorbital oedema, congestion, and proptosis were evident in OD, and intraocular pressure was recorded as 26 mmHg using Goldmann applanation tonometry under prostaglandin analogue treatment. Eye movements were normal in OS and moderately restricted in OD, particularly in upgaze, and exotropia was present.

Maxillofacial and orbital magnetic resonance imaging (MRI) revealed a mostly homogeneous malignant soft tissue lesion extending from the retro-orbital area to the orbital apex, ethmoid cells, and nasal cavity. The lesion extended posteriorly to the level of the choana and inferolaterally to the maxillary sinus. It had invaded the medial and inferior rectus muscles and, in some areas, the intraorbital optic nerve. No lacrimal gland involvement was observed (Fig. 1).

Otorhinolaryngological examination appeared normal, except for a polyp-like lesion extending from the middle to the inferior meatus in the right nasal cavity. Positron emission tomography–computed tomography (PET-CT) detected fluorodeoxyglucose uptake generally consistent with the lesion seen on MRI. There was no extralesional signal increase indicating metastasis.

The patient underwent tumour excision combining endoscopic sinus surgery with an inferior transconjunctival approach. The lesion was accessed endonasally, and the involved posterior maxillary sinus, anterior and posterior ethmoid cells, and lamina papyracea were carefully debrided. The intraorbital component was then excised up to the orbital apex through an inferior transconjunctival incision. The mass was removed with a Tru-Cut instrument and a microdebrider. Adjacent bony structures were drilled as needed to achieve adequate clearance. No postoperative ophthalmological or otorhinolaryngological complications were observed. Histopathological examination of both surgical excision specimens (nasal and intraorbital) was consistent with ACC (Fig. 2), demonstrating a predominantly cribriform growth pattern characterized by pseudocystic spaces surrounded by basaloid tumour cells, with no evidence of perineural invasion in the examined sections.

The patient underwent adjuvant radiotherapy because lesions were detected on postoperative maxillofacial and orbital MRI scans, which suggested the presence of residual tumour in the surgical area. The post-treatment course was uneventful for 10 months.

Discussion

ACC is a relatively rare, aggressive, and destructive malignant tumour. It was first described by Robin, Lorain, and Laboulbene in two papers published in 1853 and 1854. Later, Theodor Bilroth referred to it as "Cylindroma" in 1856. In 1966, Friedmann and Osborn described this tumour as "Cribriform Adenocarcinoma," highlighting its potential to behave as both an epithelial and a connective tissue malignancy (5,6). The current term "Adenoid Cystic Carcinoma" was introduced by Reid in 1952 (7).

Although it predominantly arises from the salivary glands and lacrimal gland, approximately 10%–25% of cases arise from the sinonasal cavity and paranasal sinuses (8). The slow-growing nature of the tumour, its asymptomatic progression, and its potential for perineural invasion make diagnosis and management challenging. In most cases, by the time of diagnosis, the tumour has spread to vital structures such as the dura mater, brain, orbit, carotid artery, and cranial nerves. Symptoms associated with sinonasal ACC include nasal obstruction, epistaxis, rhinorrhea, facial pain, headache, and paresthesia (6,8,9).

For diagnosis, computed tomography and MRI are valuable for demonstrating the destructive pattern, extension, and invasion of the tumour. Additionally, PET-CT should be considered for evaluating distant metastasis. Fine-needle aspiration biopsy and histopathological examination of surgical excision material can be used for tissue diagnosis (10,11). Polymorphous adenocarcinoma, basaloid squamous cell carcinoma, adenosquamous carcinoma, and small cell neuroendocrine carcinoma should be considered in the differential diagnosis (12).

Among the treatment methods, surgical excision followed by radiotherapy is the best option in terms of overall

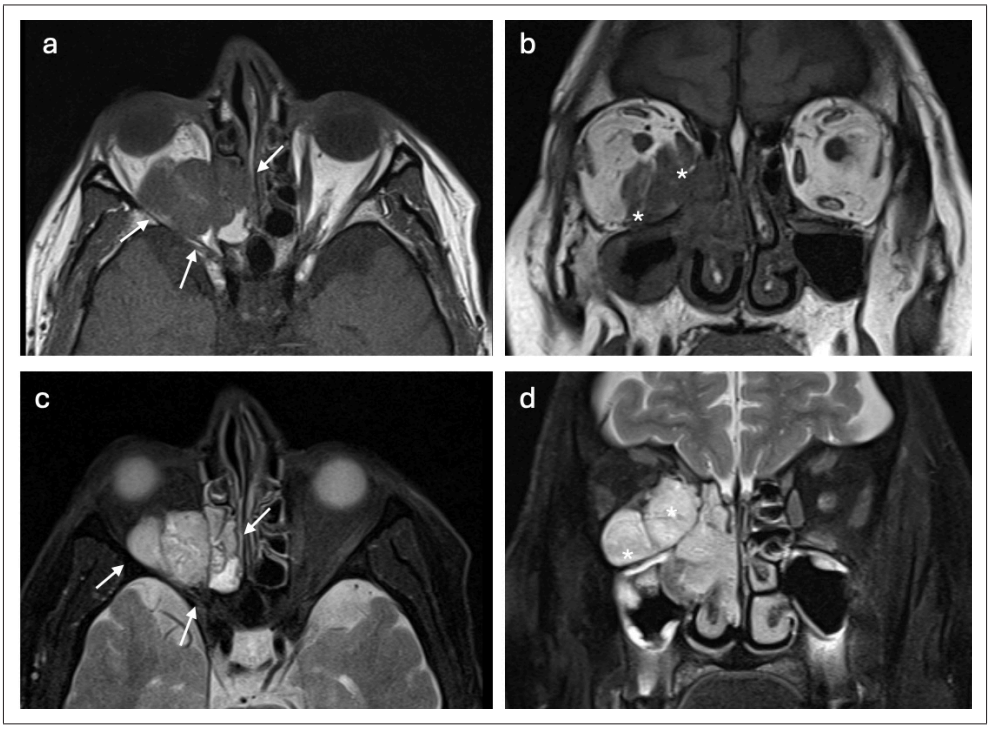

Figure 1. Maxillofacial and orbital MRI sections of the tumour. A homogeneous lesion extending from the retro-orbital area to the orbital apex, ethmoid cells, and nasal cavity was observed (see arrows). There was infiltration in the medial and inferior rectus muscles (see asterisks) and occasionally in the optic nerve: **a)** T1 axial, **b)** T1 coronal, **c)** T2 axial, **d)** T2 coronal.

survival and disease control. The surgical method varies depending on the size, spread, and accessibility of the tumour. However, functional endoscopic sinus surgery is generally the preferred approach for treating sinonasal ACCs (13).

Orbital involvement typically occurs in tumours originating from the lacrimal gland or as a result of local spread from the paranasal sinuses. ACC accounts for approximately 1% of orbital tumours and often appears as a superotemporal mass originating from the lacrimal gland, resulting in periocular pain, ptosis, and/or proptosis (14). Isolated orbital adenoid cystic carcinoma without another primary focus is extremely rare, with only a few cases documented in the literature. Shields et al. reported an isolated anteronasal orbital ACC in a 26-year-old man, suggesting that the tumour originated from ectopic lacrimal gland tissue within the medial orbit (15). Lin et al. described a case of ACC involving the inferior orbit through the inferior rectus muscle with no evidence of lacrimal gland involvement (16). Venkitaraman et al. reported a case of ACC affecting the orbital apex and extending into the cranial cavity, without involvement of the lacrimal gland or sac, in a 51-year-old man (17). Walsh et al. documented primary ACC in the orbital apex and cavernous sinus in a 53-year-old woman with progressive visual loss (18). Pattabiraman et al. reported a case that mimicked an intraconal

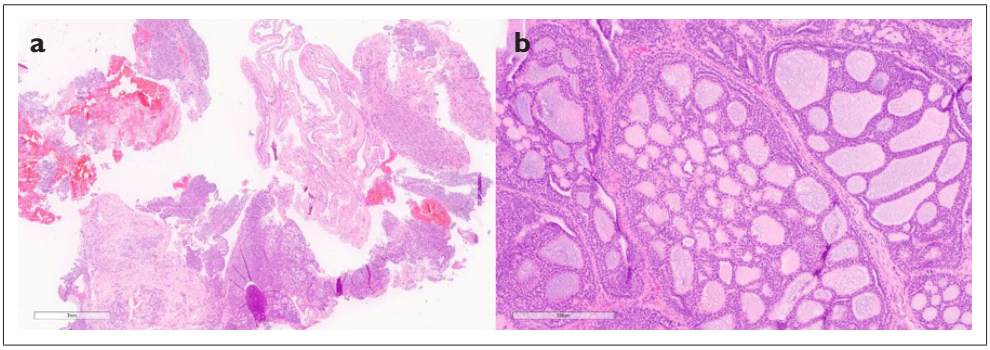

Figure 2. Histopathological images of surgical excision material, Haematoxylin and eosin staining: **a)** 2x **b)** 10x.

lesion but was confirmed to be ACC both radiologically and histopathologically (19). They suggested that the lesion was located in this area through perineural invasion. Finally, Kwon et al. reported sinonasal ACC in the medial orbit of a 61-year-old male patient with a history of prior sinus surgery (3). They suggested that the presenting pathology was a secondary manifestation resulting from perineural spread from the sinuses.

The presented case exhibited oedema, hyperaemia, proptosis, exophthalmos, and vision loss in the right eye for approximately 4 months, resembling the findings of a retrobulbar mass. Although there were no otorhinolaryngological complaints, a polyp-like lesion was detected in the right nasal cavity. Imaging findings indicated a malignant pathology extending from the retroorbital area to the orbital apex, ethmoid cells, and nasal cavity. The surgical excision material from both the orbit and nasal cavity suggested ACC. No clinical or radiological involvement of the lacrimal gland was observed in this case. The clinical presentation in this case may represent an extension of sinonasal ACC into the orbit or may result from isolated primary orbital involvement. Although rare, isolated orbital ACC has been reported in the literature. The patient underwent endoscopic sinus surgery and tumour excision via an inferior transconjunctival approach. Postoperative imaging revealed residual lesions, which were treated with adjuvant radiotherapy. No recurrence was observed during the 10-month follow-up period. However, given the well-known potential for late recurrence and delayed metastasis in ACC (20), the relatively short follow-up period represents a limitation of this report.

Conclusion

In conclusion, sinonasal ACC may present as an isolated retrobulbar mass. This report aims to provide insight into this tumour for both ophthalmologists and otolaryngologists, emphasizing the importance of a multidisciplinary approach and histopathological diagnosis.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consents were obtained from patient and his family.

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Case Report

Assessing Multi-Modal Imaging for Late Capsular Bag Distension Syndrome: A Study of Two Clinical Cases

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Abstract

We report two cases of late capsular bag distension syndrome (LCBDS), which is a rare but significant complication following cataract surgery and often presents with blurred vision years after intraocular lens (IOL) implantation. Case 1: An 80-year-old male presented with a one-year history of progressive blurred vision in the right eye. His history included uneventful phacoemulsification and multifocal IOL implantation eight years earlier. Examination revealed dense, turbid fluid behind the IOL. Scheimpflug imaging and anterior segment optical coherence tomography (AS-OCT) detected hyperintense signals between the IOL and posterior capsule. Nd:YAG laser posterior capsulotomy was performed, resulting in complete resolution of the fluid and recovery of 20/20 vision. Case 2: A 60-year-old hypertensive female reported progressive blurred vision in the right eye for nine months. Ten years earlier, she had undergone uncomplicated cataract surgery. AS-OCT and Scheimpflug imaging demonstrated fluid accumulation posterior to the IOL. Nd:YAG capsulotomy led to complete symptom resolution and restoration of 20/20 vision at the one-week follow-up. This report is among the few in the literature to demonstrate how multimodal imaging, particularly AS-OCT and Scheimpflug imaging, can distinctly differentiate late capsular bag distension syndrome from posterior capsule opacification, enabling accurate diagnosis and appropriate management.

Keywords: Capsular distension, multimodal imaging, Nd:YAG laser

Introduction

Late capsular bag distension syndrome (LCBDS) is a rare, late postoperative manifestation of capsular block syndrome characterized by the accumulation of turbid/milky fluid between the intraocular lens (IOL) and posterior capsule. Its frequency after phacoemulsification with in-the-bag IOL implantation has been reported to be around 0.7–1.0% in the literature, highlighting its uncommon nature (1). Presentation may occur months to decades after cataract surgery, with ultra-late cases reported up to 33 years (2). In some cases, biomicroscopic examination alone may not be sufficient for diagnosis, and the condition can be confirmed using various imaging modalities. Nd:YAG posterior capsulotomy is considered first-line therapy and is usually effective, while surgical approaches, such as pars plana vitrectomy, may be required in refractory or complicated cases (1). We report two illustrative cases of LCBDS confirmed with multimodal imaging and outline their diagnostic features and management outcomes.

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Case Report 1

An 80-year-old male presented to the ophthalmology outpatient clinic with a gradual decline in vision in his right eye over the span of one year. He had previously undergone uncomplicated cataract surgery, including phacoemulsification and posterior chamber multifocal lens implantation in both eyes, eight years prior, with no reported complications thereafter. At the time of presentation, his corrected distance visual acuity (CDVA) was recorded as hand motion in the right eye and 20/20 in the left eye, with an intraocular pressure (IOP) of 13 mmHg in both eyes. Autorefractor (AR) values were -0.25 (105 -1.75) in the right eye and +1.75 (94 -1.00) in the left eye. Slit-lamp biomicroscopy revealed pseudoexfoliation (PX), and poor pupillary dilation was noted bilaterally. In the right eye, a milky opacity between the lens and the posterior capsule was observed, with no signs of inflammation in the anterior chamber or vitreous (Fig. 1). Despite the difficulty in visualizing the fundus, B-scan ultrasound imaging showed normal findings.

Multimodal imaging, including Scheimpflug camera imaging (OCULUS Pentacam HR) and anterior segment spectral-domain OCT (AS-OCT) (Optovue RTVue-100, Optovue Inc., Fremont, CA, USA), demonstrated hyperintense signals between the posterior chamber intraocular lens and the posterior capsule. Subsequent Nd:YAG capsulotomy was performed for treatment. Postoperatively, the patient was prescribed topical timolol maleate 0.5% twice daily, topical prednisolone acetate 1.0% ophthalmic solution four times daily, and cyclopentolate HCl 1% drops twice daily to prevent inflammation and elevated intraocular pressure.

On the first postoperative day, CDVA improved to 16/20, IOP was 24 mmHg, +1 anterior chamber cell was noted, the milky fluid had dissipated, and fundus examination was normal. By the first-week follow-up, CDVA had returned to 20/20, IOP was 12 mmHg, and AR readings were +0.25 (110 -2.25). Anterior chamber inflammation had resolved, and AS-OCT and Scheimpflug images confirmed the resolution of milky fluid accumulation (Fig. 2). At subsequent visits, visual acuity remained 20/20, intraocular pressure normalized, and anterior segment and fundus examinations were unremarkable.

Case Report 2

A 60-year-old female patient presented to the outpatient clinic with complaints of decreased vision in her right eye for the past nine months. Her medical history revealed uneventful cataract surgery 10 years prior, and the patient had a known diagnosis of hypertension.

Upon examination, CDVA was measured as 12/20 in the right eye and hand motion in the left eye, and IOP was 13/15 mmHg in the right and left eyes, respectively. AR readings were -0.25 (140 -1.00) in the right eye and -5.50 in the left eye. Slit-lamp biomicroscopic examination revealed opacity behind the IOL in the right eye without signs of inflammation in the anterior chamber or vitreous. The red reflex was absent, and a mature cataract was observed in the left eye. Ultrasonography demonstrated normal retinal findings in both eyes. Cataract surgery was planned for the left eye.

In the right eye, AS-OCT and Scheimpflug imaging revealed milky opacification behind the intraocular lens, and an Nd:YAG laser posterior capsulotomy was performed. Following the procedure, the patient was prescribed topical timolol maleate 0.5% twice daily and topical prednisolone acetate 1.0% ophthalmic solution eight times daily. On the first postoperative day, CDVA improved to 20/20, IOP was 12 mmHg, and mild (+1) anterior chamber and vitreous cells were noted. The milky fluid had completely dissipated. At the first-week follow-up, CDVA remained 20/20, IOP was 12 mmHg, and AR values were +0.00 (165 -050). At the three-month follow-up, no complications were observed. We performed phacoemulsification surgery for the left eye one week later.

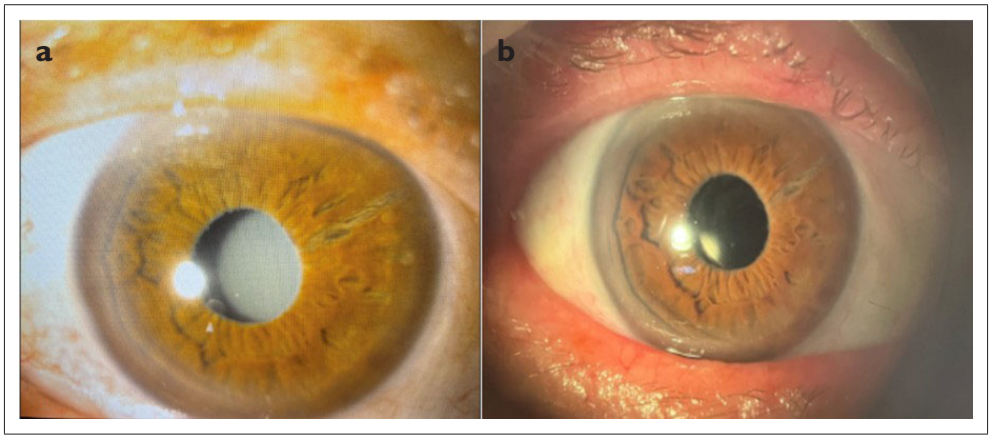

Figure 1. a) Pre-treatment slit-lamp photograph showing white deposits behind the lens. **b)** Post-treatment slit-lamp photograph showing complete resolution after Nd:YAG laser capsulotomy.

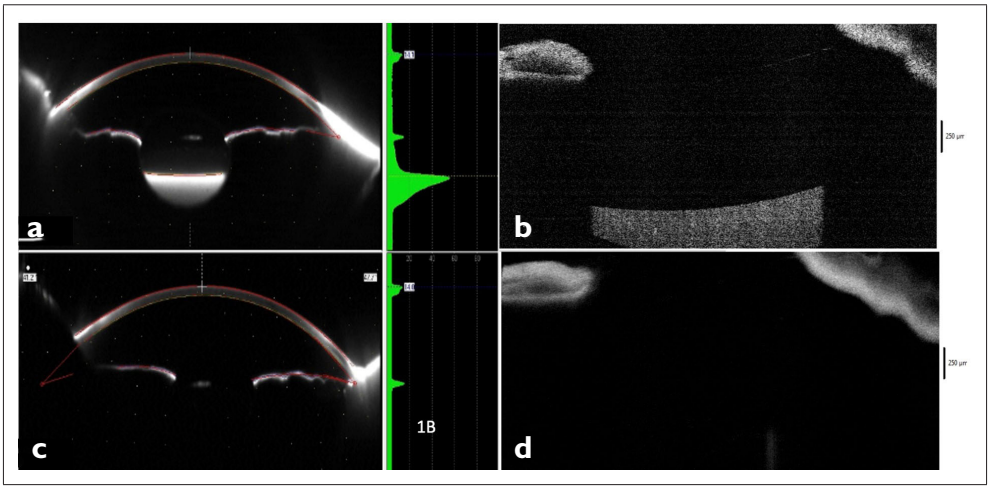

Figure 2. a) Pre-treatment Scheimpflug imaging showing deposits. **b)** Post-treatment image demonstrating resolution. **c)** AS-OCT pre-treatment appearance. **d)** AS-OCT post-treatment appearance.

Discussion

In this report, we presented two cases of LCBDS, detailing their clinical features and treatment approach. Our findings support the existing literature, demonstrating that AS-OCT and Scheimpflug imaging are valuable diagnostic tools when slit-lamp biomicroscopy is insufficient for confirming the diagnosis. Furthermore, we observed that Nd:YAG laser posterior capsulotomy is a safe and effective treatment option for managing late-onset CBDS.

CBDS has been reported after uncomplicated phacoemulsification surgery with continuous curvilinear capsulorhexis (CCC); however, it has rarely been reported with can-opener capsulorhexis (3). Miyake et al. characterized the syndrome according to the time of onset as intraoperative, early postoperative, and late postoperative (4). CBDS develops when the periphery of the capsulorhexis firmly attaches to the anterior surface of the IOL, forming a closed chamber between the intraocular lens and the posterior lens capsule. This leads to the accumulation of cloudy to milky white fluid. While the exact source of this fluid is uncertain, it is believed that metaplastic changes in residual lens epithelial cells result in the production of collagen and other extracellular matrix materials (5). Although CBDS is most commonly observed in eyes with in-the-bag posterior chamber IOLs, a recent report described its occurrence with a sulcus-placed IOL, highlighting that the condition may develop in various lens positions (6). In our case, however, CBDS developed in an eye implanted with a multifocal posterior chamber IOL, a presentation that, to the best of our knowledge, has not been previously documented in the literature. This observation suggests that CBDS may also occur with premium multifocal IOLs, and clinicians should remain alert to this possibility when evaluating postoperative visual decline. CBDS development is associated with various risk factors, such as the retention of ophthalmic viscoelastic devices, insufficient removal of subincisional cortex, juxtaposition of the IOL and capsular bag, postoperative inflammation, and IOL sequestration due to Propionibacterium acnes infection (1,7). Recent studies have reported that cytokines such as interleukin-1, VEGF, IL-8, and VCAM may be effective in CBDS (8,9). Except for the presence of PEX in our first case, no additional risk factors were identified in either patient. Although a recent publication did not list PEX among the established risk factors for CBDS (2), it may indirectly contribute by increasing the likelihood of an uneven or incomplete capsulorhexis, thereby predisposing to this condition.

CBDS may lead to decreased visual acuity and myopic refractive changes. However, this condition can be successfully treated with Nd:YAG laser treatment (9). Symptoms may develop in the early or late postoperative period, and CBDS has been reported up to 20 to 33 years after cataract surgery (2,11). In our cases, symptoms developed 8 and 10 years after cataract surgery, consistent with a late-onset presentation.

While slit-lamp biomicroscopy may raise suspicion, it is often insufficient for confirmation. Various diagnostic modalities have been used to diagnose CBDS, including slit-lamp biomicroscopy, ultrasound biomicroscopy (UBM), AS-OCT, and Scheimpflug-based photography (12-14). In our cases, we employed multimodal imaging with AS-OCT and Scheimpflug multimodal imaging techniques to visualize the fluid and its subsequent disappearance after Nd:YAG laser treatment. These methods are noninvasive, reproducible, and feasible in routine practice. Recently, Jeria et al. demonstrated distinct SS-OCT features of CBDS, suggesting that, with ongoing technological progress, high-resolution multimodal imaging will become increasingly accessible for accurate diagnosis and postoperative monitoring (15).

Nd:YAG laser treatment, encompassing anterior and posterior laser capsulotomy, is widely recommended as the primary approach for addressing late-onset CBDS (16-19). However, potential disadvantages of Nd:YAG laser capsulotomy include elevated IOP, posterior capsule wrinkling, and a high recurrence rate, which present challenges in effective management. Additionally, severe complications such as P. acnes-associated endophthalmitis, dense opaque substance accumulation, and extensive posterior capsule expansion can complicate the procedure, leading some clinicians to prefer surgical intervention (20-22).

Considering factors such as surgical risk, cost considerations, and ease of application, we opted for Nd:YAG laser intervention in our cases. We chose to follow up with the patients at short intervals to monitor for potential increases in intraocular pressure, inflammation, or endophthalmitis. In Case 1, on the first day, there was +1 cell in the anterior chamber, and IOP was 24 mmHg, which quickly regressed with treatment and returned to the normal range. In Case 2, postoperative topical medication was prescribed, and IOP was 12 mmHg on the first postoperative day. Prescribing topical medication after Nd:YAG laser treatment may prevent transient intraocular pressure elevation associated with inflammation. In case presentations of CBDS, the most feared complication of treatment is the possibility of undetected Propionibacterium acnes and the subsequent development of endophthalmitis. We were unable to obtain a sample from the anterior chamber and were therefore unable to demonstrate the absence of Propionibacterium acnes. In cases with high suspicion, to minimize the possibility of Nd:YAG laser-induced Propionibacterium dissemination and endophthalmitis, 25-gauge pars plana vitrectomy with posterior capsulotomy may be considered (21). Our decision to perform Nd:YAG capsulotomy in these cases was based on the absence of anterior chamber or vitreous inflammation indicative of Propionibacterium infection. This decision was further supported by current evidence indicating that this treatment option is safe, effective, and appropriate, without the associated risks of a more invasive pars plana approach. Throughout the follow-up period, our patients did not experience severe complications such as uncontrollable IOP elevation, uveitis, endophthalmitis, cystoid macular edema, or retinal detachment.

Conclusion

Our study highlights the diagnosis of LCBDS as a rare cause of decreased vision occurring long after uneventful cataract surgery. Only a limited number of such cases have been reported in the literature, underscoring the rarity of this condition. When slit-lamp biomicroscopy does not provide a clear diagnosis, multimodal anterior segment imaging, including AS-OCT and Scheimpflug photography, serves as a valuable adjunct for confirming the presence and extent of intracapsular fluid accumulation. Although Nd:YAG laser posterior capsulotomy generally yields favorable outcomes, this intervention should be performed only in the absence of clinical suspicion for Propionibacterium acnes infection.

Disclosures

Ethics Committee Approval: These are case reports, therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consents were obtained from both patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.A.T., G.D.G.; Design: S.A.T., G.D.G.; Supervision: S.A.T.; Resource: G.O., G.D.G.; Materials: G.O., G.D.G.; Data Collection and/or Processing: G.O.; Analysis and/or Interpretation: S.A.T., G.D.G. ; Literature Search: G.O., G.D.G., S.A.T.; Writing: G.D.G., S.A.T.; Critical Reviews: S.A.T.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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