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AT A GLANCE

2025 Issue 5 at a Glance:

Esteemed colleagues,

This issue of our journal includes an editorial, four original research articles, one meta-analysis, one review, one case report, and three letters to the editor.

In their editorial article titled "AI in the Editorial Office: From Artificial Narrow to General Intelligence in Scientific Publishing", Özdemir and Kırık address two major problems in academic publishing: the increasing publication volume and the slowness of the current system. They discuss the drawbacks of artificial narrow intelligence used by some publishers to address these issues, as well as the artificial narrow intelligence models used by referees, suggesting that these problems could be solved in the future through the development and integration of artificial general intelligence models that have clearly defined standards and boundaries and remain centered around human oversight ([See pages 237-238](#)).

Erbezci et al. report a study evaluating foveal lesion and preferred retinal locus (PRL) positions and their impact on visual acuity in patients with juvenile macular dystrophy (JMD). They showed that PRLs were most frequently located superiorly or nasally in JMD, with a significant relationship between PRL location and patient age. The authors emphasized that cortical adaptation mechanisms play a role in the age-related relocation and optimization of PRLs, pointing out the potential benefit of harnessing or directing that adaptation in clinical practice ([See pages 239-244](#)).

In their study to evaluate the refractive outcomes of cataract surgery in eyes with keratoconus and compare the performance of the SRK/T and Kane formulas in intraocular lens power calculation, Akbaş et al. reported that there was no significant difference between the two formulas in early keratoconus cases, whereas the Kane formula gave more accurate results than SRK/T in advanced keratoconus cases ([See pages 245-248](#)).

Yargı Özkoçak and Altan conducted a survey study assessing current clinical practices and expert opinions in uveitic cataract surgery in order to identify areas of agreement and divergence. They determined that there was strong consensus on issues such as ensuring a 3-month inflammation-free period preoperatively, continuing conventional immunosuppressive treatment without dose adjustment, and preferring hydrophobic acrylic intraocular lenses in juvenile idiopathic arthritis-associated uveitis. However, there was notable divergence in preoperative topical steroid use, nonsteroidal anti-inflammatory drug prophylaxis for cystoid macular edema, and strategies for managing postoperative relapses ([See pages 249-255](#)).

Kapran et al. evaluated the reliability and effectiveness of a new modification using a 25/32-gauge subretinal cannula for subretinal fluid drainage in pars plana vitrectomy surgery applied for the treatment of rhegmatogenous retinal detachment, and concluded that this technique could be a safe and effective alternative compared to other internal drainage techniques ([See pages 256-259](#)).

In a meta-analysis study evaluating the effectiveness of different screening methods utilizing artificial intelligence-based tools, portable fundus cameras, and non-ophthalmologist trained personnel in the detection of diabetic retinopathy in developing countries, Yüdistira et al. showed that both non-mydriatic and mydriatic imaging performed well and have become promising options for large-scale screening ([See pages 260-275](#)).

Hyaluronic acid (HA) injections are a generally safe and reversible method frequently used to treat signs of aging in the periorbital region. In this issue's review, Nalcı Baytaroglu and Hoşal provide readers with a detailed analysis of the incidence, risk factors, pathophysiology, symptoms, and findings of complications associated with cosmetic periorbital HA injections, their treatment methods, and hyaluronidase indications, dosage, and safety profile ([See pages 276-286](#)).

Dertsiz Kozan et al. examined the clinical findings of two siblings with familial feline leukemia virus subgroup C receptor1 (FLVCR1) mutation and describe a new phenotype, neurotrophic keratopathy ([See pages 287-290](#)).

Sustainability and reducing the carbon footprint of health services have become increasingly important in recent years. Dertsiz Kozan and Bayraktar propose in their letter to the editor that providing eye drops as box-free bottles with digital package inserts and encouraging patients to recycle the empty bottles will make a valuable contribution in terms of environmental sustainability and patient-oriented care ([See pages 291-292](#)).

In another letter to the editor, Günay et al. share their treatment approach to a case of bilateral choroidal neovascularization caused by laser pointer exposure. The authors note the increased incidence of such injuries among children especially and emphasize the need for public education and stricter regulation of hand-held lasers ([See pages 293-295](#)).

Respectfully on behalf of the Editorial Board,
Özlem Yıldırım, MD



AI in the Editorial Office: From Artificial Narrow to General Intelligence in Scientific Publishing

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Academic publishing is indispensable for the generation, validation, and dissemination of information. Publishing research results through a peer-review process ensures the reliability and quality of scientific literature. Each published study contributes to the body of knowledge in its field and allows findings to be shared on a global scale. Journals foster academic competition among researchers by serving as benchmarks for career development, citation, and scientific reputation.¹ However, the academic publishing industry is under increasing publication pressure. According to PubMed data, the annual number of publications grew from 532,000 in 2000 to over 1.7 million in 2024, and consider also that the number of manuscripts submitted to journals far exceeds the number published.² Because of this increasing volume, the submission-to-publication timeline can last years in some cases. Disseminating information before it becomes outdated is essential for both journals and researchers. However, the process is centered around human labor. The importance of peer reviewers in particular, who contribute on a purely voluntary basis, cannot be overstated. The ever-growing volume of publications primarily increases the burden on reviewers but also negatively impacts other time-consuming, labor-intensive steps such as pre-screening, editorial tracking, language editing, and formatting.

Keywords: Agentic artificial intelligence, scientific publishing, peer review, artificial narrow intelligence, artificial general intelligence

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Artificial intelligence (AI) models that automate tasks requiring human intelligence hold significant transformative potential in this context. Most current AI can be categorized as artificial narrow intelligence (ANI), which focuses on specific tasks.³ In academic publishing, the use of ANI is currently limited to some publishers' submission-stage checks (e.g., grammar/format control, plagiarism screening, verification of mandatory sections) and reviewer recommendations. Tools that evaluate academic content have also been developed independently of publishing houses. However, both publishers and editorial boards remain cautious about integrating AI into the peer-review process because of concerns such as the models' capacity for in-depth scientific analysis, their lack of access to the entire body of literature, the potential for data-driven bias, the confidentiality of unpublished data, and most importantly, the absence of human-like multidimensional reasoning. In contrast, a dangerous practice is becoming increasingly common. Authors have reported that some peer reviewers are using general-purpose large language models in their evaluations.⁴ More alarmingly, their output is sometimes accepted as absolute truth, without critical oversight, and submitted as the reviewer's report. As these models can present misinformation in highly persuasive language (a phenomenon known as "hallucination") and lack advanced reasoning capabilities, their uncontrolled use raises serious ethical and credibility issues that could undermine the foundations of academic publishing. The solution lies not in the uncontrolled use of general-purpose models, but in the development of purpose-built AI systems tailored for academic publishing through collaboration with publishers and journals. An AI model integrated into the peer-review process must be transparent and explainable, have bias auditability and access to the relevant literature, ensure data security, and crucially, maintain a "human-in-the-loop" structure. Such a system could alleviate the workload by pre-analyzing aspects like originality, contribution to the literature, methodology, statistical analysis, and ethical compliance. It could also help systematically address points that reviewers might overlook due to heavy workloads or low motivation, thereby improving the quality of evaluations.

The next step in this vision involves agent-based (agentic) AI systems. Agentic AI consists of multiple specialized ANI models that can make decisions autonomously to achieve specific goals.³ A specialized agentic AI for academic publishing could act as a conductor, coordinating many steps of the process: a *Triage Agent* would analyze the manuscript, check for plagiarism and formatting, and identify suitable editors and reviewers; a *Methodology Agent* would inspect statistical consistency, experimental design, and ethical compliance; a *Literature Agent* would evaluate originality and novelty by comparing citations and findings with the existing literature; and a *Communication Agent* would automate correspondence between authors, editors, and reviewers. The harmonious operation of these autonomous agents has the potential to significantly shorten publication timelines. Nevertheless, these systems cannot replace the human creativity and critical judgment essential for peer evaluation. Therefore, human oversight remains indispensable.

The next true revolution may come with the development of artificial general intelligence (AGI), a theoretical system capable of mimicking all aspects of human intelligence. Although AGI does not yet exist, many technology companies are working intensively toward this goal, and it has been suggested that next-generation models like GPT-5 could be a significant step on the path to AGI.^{3,5} AGI could offer capabilities beyond deep scientific and philosophical analysis, such as detecting data fabrication, proposing novel research avenues, and testing findings through simulations where appropriate. It could also accelerate the publishing workflow by automating standard processes other than peer review. However, it remains uncertain when and under what conditions AGI will come to fruition.

In conclusion, the increasing volume of submissions and the inefficiencies of the current system make the integration of AI into academic publishing inevitable. This integration must not proceed in an uncontrolled manner, but managed using

an approach with clearly defined standards and boundaries, remaining centered around human oversight. In the current landscape, purpose-built multimodal AI tools can facilitate the workflow of authors and editors, saving time and effort while accelerating scientific progress. Guiding this transformation via consensus among publishers, editors, and other stakeholders will be essential to safeguarding the reliability and quality of scientific communication in the future.

Declarations

Authorship Contributions

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Preferred Retinal Locus in Juvenile Macular Dystrophy

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Abstract

Objectives: To evaluate foveal lesion and preferred retinal locus (PRL) locations and their effects on visual acuity in juvenile macular dystrophy (JMD) patients.

Materials and Methods: In this retrospective study, 14 JMD patients (28 eyes) with bilateral central vision loss were examined using scanning laser ophthalmoscope/optical coherence tomography. Best-corrected visual acuity (BCVA), dimensions and location of the macular lesion, PRL location, and PRL stability were evaluated.

Results: Mean BCVA was 0.84 ± 0.17 logarithm of the minimum angle of resolution. PRL was superiorly located in 64.3% of eyes and nasally located in 35.7%. PRL location was significantly associated with patient age ($r=0.541$, $p=0.002$); nasally located PRLs were more common in younger patients (mean age 15.1 ± 2.8 years) while superiorly located PRLs were more common in older patients (mean age 22.4 ± 6.9 years). Superiorly located PRLs were significantly closer to the fovea than nasally located PRLs ($p=0.014$). Visual acuity worsened as lesion size increased and PRL-fovea distance increased. PRL-fovea distance was longer in younger patients and positively correlated with lesion dimensions and PRL-lesion distance.

Conclusion: In JMD patients, PRLs are predominantly located superiorly or nasally. In younger patients, PRLs are typically located nasally and farther from the fovea, with poorer visual acuity compared to older patients. Cortical adaptation mechanisms may play a role in changing PRL location with age. Understanding PRL characteristics in JMD is crucial for developing effective low-vision rehabilitation strategies.

Keywords: Macula, juvenile macular degeneration, central scotoma, low vision

Introduction

Juvenile macular dystrophy (JMD) is characterized by bilateral central vision loss due to macular lesions that cause central scotoma and severely affect foveal function.^{1,2} As a compensatory mechanism, patients frequently develop eccentric fixation areas, known as preferred retinal loci (PRLs). These are healthier parts of the eccentric retina used as alternative fixation points for visual tasks like reading and identifying faces and objects.³ Crossland and Rubin⁴ defined PRLs as “one or more circumscribed regions of functioning retina, repeatedly aligned with a visual target for a specified task, that may also be used for attentional deployment and as the oculomotor reference.” The location and stability of PRLs play a critical role in determining visual acuity, fixation stability, and rehabilitation outcomes.^{5,6}

Although it has been recognized that a PRL can be positioned differently in various macular pathologies or for different visual tasks, detailed characterization of PRL patterns in JMD patients remains limited. Microperimetry has emerged as a valuable tool for evaluating the location and stability of fixation in these patients.^{2,7} This study aimed to fill this knowledge gap by retrospectively evaluating foveal lesion and PRL locations and their effects on visual acuity in JMD patients assessed with scanning laser ophthalmoscope (SLO)/optical coherence tomography (OCT).

Materials and Methods

The study protocol adhered to the tenets of the Declaration of Helsinki, with approval obtained from the Ethics Committee of Dokuz Eylül University (date: 23.06.2021, approval number: 2021/19-22 [6371-GOA]). We retrospectively evaluated the records of JMD patients referred to our clinic for low-vision rehabilitation. Informed consent was waived due to the retrospective nature of the study. Included patients were below 35 years of age with bilateral impairment of central vision due to macular lesions. We excluded patients with other eye diseases

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affecting visual acuity, those with a family history of other inherited systemic or retinal diseases, and those with incomplete records. In total, 14 JMD patients (28 eyes) with central vision loss were enrolled.

Distance best-corrected visual acuity (BCVA) was evaluated using the Early Treatment Diabetic Retinopathy Study Chart (Lighthouse, Long Island, NY, USA), and the results were expressed as the logarithm of the minimum angle of resolution (logMAR).

All patients were evaluated monocularly with an Optos SLO/OCT/microperimetry device (Optos, Florida, USA). Previous studies have also employed SLOs and SLO-based microperimetry to analyze PRL features in hereditary macular diseases such as Stargardt disease.^{8,9,10,11,12,13} JMD-related lesions and PRLs were assessed at the beginning of their low-vision clinical evaluation. For this purpose, patients were asked to fixate on a 2° cross target for 5 seconds. The device software continuously tracked fixation while the examiner simultaneously observed the fundus and fixation behavior. The system displayed fixation points as a cluster of cross marks on the fundus image. The dispersion of these marks indicated the fixation area. The greatest distance between any two marks was taken as the measure of fixation stability, with larger values reflecting greater instability of the PRL. This approach, although different from the bicurve ellipse area or percentage-within-1°/2° methods, has been applied in previous clinical studies (Figure 1).⁷

Lesion size was assessed by measuring the largest vertical and horizontal diameters, and the surface area was calculated under

the assumption of an ellipsoid shape, providing a standardized comparison across patients.

We marked the fovea as 15.5 degrees horizontally and 1.3 degrees vertically from the center of the optic disc.¹⁴ Considering the fovea as the center, we divided the retina into quadrants and classified PRL location relative to the fovea as superior (from 45°-135°), inferior (225°-315°), temporal (135°-225°), or nasal (315°-45°) (Figure 2).

Measurements were taken in units of degrees with the built-in caliper, and the units were converted to millimeters, considering one degree of visual angle equals 288 µm on the retina.¹⁵ The same physician conducted all evaluations to minimize variation in the measurements.

Statistical Analysis

SPSS version 22.0 statistical software (IBM Corp., Armonk, NY) was used for statistical analyses. The Shapiro-Wilk normality test assessed distribution uniformity. For non-normally distributed data, parametric tests were enabled through logarithmic correction. Non-parametric data were expressed as medians and ranges, and parametric data as mean ± standard deviation. P values <0.05 were considered statistically significant. Pearson correlation analysis, Student's t-tests, and chi-square test were used for statistical analyses. Pearson correlation analysis examined relationships among lesion dimensions, PRL location and stability, and logMAR BCVA.

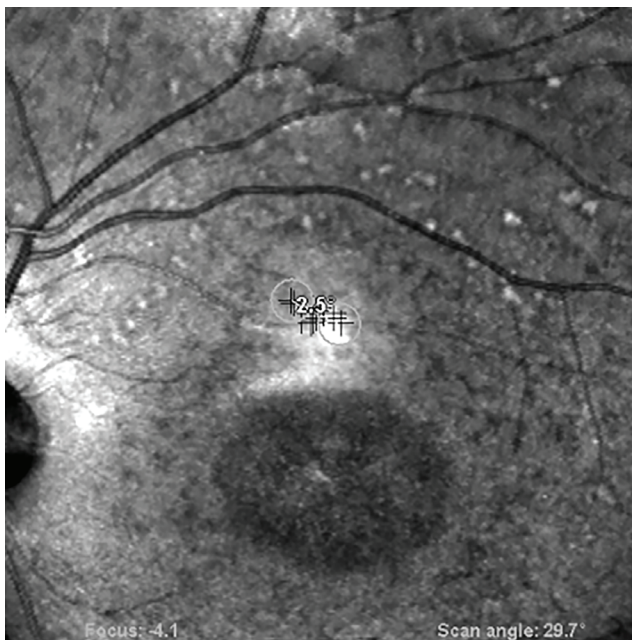


Figure 1. Example of fixation stability measurement in a patient with juvenile macular dystrophy. Fixation points recorded during a 5-second task are displayed as cross marks superimposed on the fundus image. The dispersion of the marks indicates fixation stability, quantified as the maximum distance between the two most distant points

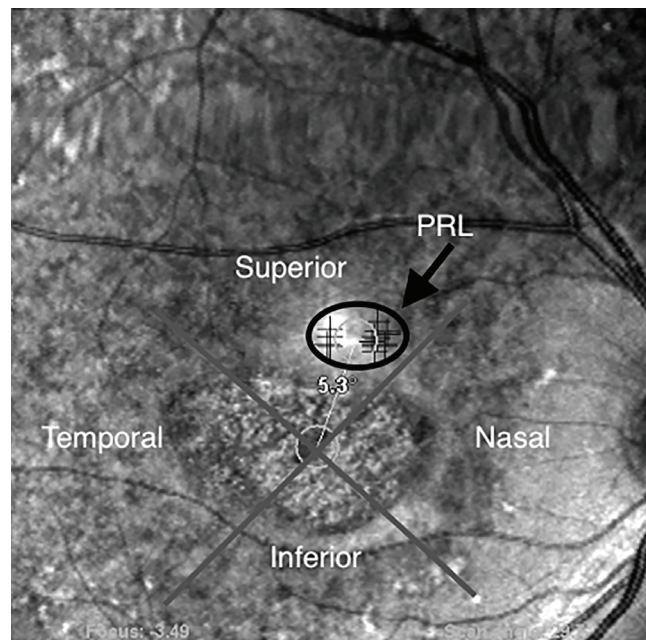


Figure 2. Determination of preferred retinal locus (PRL) location relative to the fovea in a patient with juvenile macular dystrophy. The fovea was marked at 15.5° horizontally and 1.3° vertically from the center of the optic disc. Using the fovea as the reference point, the retina was divided into four quadrants: superior (45°-135°), inferior (225°-315°), temporal (135°-225°), and nasal (315°-45°). Each PRL was classified according to its location in one of these quadrants

Results

Among the 14 patients, 8 were male and 6 female, with a mean age of 19.8 ± 6.8 years (range, 12-34). All patients had significant loss of central visual acuity due to JMD. The mean BCVA was 0.84 ± 0.17 logMAR (range, 0.52-1.15). Descriptive statistics, including vertical lesion size, horizontal lesion size, lesion area, distance from edge of lesion to PRL, distance from anatomic fovea to PRL, and PRL stability are given in [Table 1](#).

Eccentric fixation was present in all examined eyes. Importantly, each eye demonstrated a single dominant PRL during the 5-second fixation task, although the possibility of secondary PRLs for other visual tasks cannot be excluded. PRL was superiorly located in 18 eyes (64.3%) and nasally located in 10 eyes (35.7%). PRL location was significantly correlated with patient age (point-biserial correlation, $r=0.541$, $p=0.002$). The mean age was 15.1 ± 2.8 years in patients with nasally located PRLs and 22.4 ± 6.9 years in patients with superiorly located PRLs.

In the 7 adolescent patients (10-18 years of age), PRLs were nasally located in both eyes, except in one patient who had a nasally located PRL in one eye and a superiorly located PRL in the other (dominant) eye. PRLs were superiorly located in both eyes of all 7 young adults (19-34 years old), except in one patient who had a nasally located PRL in the dominant eye and a superiorly located PRL in the non-dominant eye.

Superiorly located PRLs were significantly closer to the fovea than nasally located PRLs ($p=0.014$). The mean PRL-fovea distance was 10.1 ± 3.20 degrees for nasally located PRLs and 6.90 ± 2.44 degrees for superiorly located PRLs. PRL location and PRL stability were not statistically significantly related (Student's *t*-test, $p=0.071$). PRL location was not associated with BCVA, horizontal lesion dimension, vertical lesion dimension, or PRL-lesion distance ($p=0.098$, 0.195, 0.066, and 0.093, respectively).

Pearson correlation analysis revealed that logMAR BCVA was positively correlated with the vertical ($p=0.001$, $r=0.573$) and horizontal ($p=0.002$, $r=0.565$) dimensions of the foveal

lesion, elliptic surface area of the lesion ($p=0.001$, $r=0.589$), and PRL-fovea distance ($p=0.009$, $r=0.487$). This indicates that visual acuity worsened with larger lesion size and greater PRL-fovea distance. All statistically significant associations and correlation coefficients are summarized in [Table 2](#).

PRL-fovea distance and age were negatively correlated ($p=0.018$, $r=-0.443$), indicating greater distances in younger patients. PRL-fovea distance was positively correlated with horizontal lesion size ($p=0.001$, $r=0.581$), vertical lesion size ($p<0.001$, $r=0.745$), lesion area ($p<0.001$, $r=0.684$), PRL-lesion distance ($p<0.001$, $r=0.800$), and BCVA (logMAR) ($p=0.009$, $r=0.487$). PRL-fovea distance and PRL stability were not correlated ($p=0.741$, $r=-0.065$).

The elliptic area of the lesion was positively correlated with PRL-fovea distance ($p<0.001$, $r=0.684$) and BCVA (logMAR) ($p=0.001$, $r=0.589$), indicating that in patients with larger macular lesions, the PRL was located farther from the fovea and visual acuity was worse. There was no statistically significant correlation between PRL stability and any measurement.

Discussion

Our study revealed that in JMD patients, PRLs are predominantly located superiorly (64.3%) or nasally (35.7%), with PRL location significantly correlated with patient age. Patients younger than 18 years (mean age 15.1 years) typically exhibited nasally located PRLs, while young adults (mean age 22.4 years) more commonly had superiorly located PRLs. Additionally, superior PRLs were significantly closer to the fovea compared to nasal PRLs, though PRL location did not correlate with visual acuity or lesion dimensions.

Our findings regarding PRL location align with previous research. Verdina et al.¹⁶ reported superiorly located PRLs in 86% of JMD patients and nasally located PRLs in 9.6%.

Table 1. Measurements of the size and location of the macular lesion in patients with juvenile macular degeneration (n=28)

	Mean $\pm$ SD	Range
Vertical lesion size (°)	8.08 ± 3.40	2.90-15.10
Horizontal lesion size (°)	9.73 ± 3.71	2.90-16.40
Vertical lesion size (mm)	2.33 ± 0.98	0.84-4.35
Horizontal lesion size (mm)	2.80 ± 1.07	0.84-4.72
Elliptical lesion area (mm ²)	5.82 ± 4.24	0.55-16.12
PRL-lesion distance (°)	4.01 ± 1.72	2.10-8.60
PRL-lesion distance (mm)	1.15 ± 0.50	0.60-2.48
PRL-fovea distance (°)	8.03 ± 3.09	3.50-14.50
PRL-fovea distance (mm)	2.31 ± 0.89	1.01-4.18
Fixation stability (°)	2.15 ± 1.43	0.50-6.40
PRL: Preferred retinal locus, SD: Standard deviation		

Table 2. Correlations between visual function, lesion characteristics, and preferred retinal locus parameters in patients with juvenile macular dystrophy

Variables	p value	r
BCVA (logMAR) vs. vertical lesion size	0.001	0.573
BCVA (logMAR) vs. horizontal lesion size	0.002	0.565
BCVA (logMAR) vs. lesion surface area	0.001	0.589
BCVA (logMAR) vs. PRL-fovea distance	0.009	0.487
PRL-fovea distance vs. age	0.018	-0.443
PRL-fovea distance vs. horizontal lesion size	0.001	0.581
PRL-fovea distance vs. vertical lesion size	<0.001	0.745
PRL-fovea distance vs. lesion surface area	<0.001	0.684
PRL-fovea distance vs. PRL-lesion distance	<0.001	0.800
PRL-fovea distance vs. BCVA (logMAR)	0.009	0.487
Lesion surface area vs. BCVA (logMAR)	0.001	0.589
Lesion surface area vs. PRL-fovea distance	<0.001	0.684

Pearson correlation coefficients (r) and corresponding p values are reported. BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, PRL: Preferred retinal locus

Similarly, Chiang et al.¹⁷ found superiorly located PRLs in 48.3% of 59 JMD patients. Sunness et al.¹¹ reported that PRLs were located superiorly in 90% of patients with Stargardt disease, though their study population was older (mean age 34.2 years) than ours (mean age 19.8 years).

The PRL characteristics we observed in JMD differ from those typically seen in age-related macular degeneration (AMD). While AMD patients usually develop eccentric PRLs located at the border of the atrophic macular scar,^{7,18} our JMD patients showed PRLs at a greater distance from the lesion edge. The mean eccentric PRL-lesion distance in our JMD patients was 4.01 ± 1.72 degrees, similar to the 4.59 ± 2.36 degrees reported by Verdina et al.¹⁶, but notably larger than the 2.15-2.74 degrees typically reported in AMD patients.^{7,16,19,20} This suggests that a transition zone between the lesion and the PRL region is characteristic of JMD.

Interpretation and Implications

Superiorly located PRLs appear more advantageous for important visual tasks like reading and mobility. When the PRL is located above the lesion, the scotoma is positioned in the lower visual field, allowing unobstructed viewing of text lines during reading.^{21,22,23,24,25,26} Our finding that superiorly located PRLs were more common in older patients suggests that cortical adaptation mechanisms may play a role in PRL development and optimization over time.^{13,26}

The negative correlation between age and PRL-fovea distance, with younger patients exhibiting PRLs farther from the fovea and poorer visual acuity, likely reflects underlying structural differences. In our cohort, younger patients generally had larger lesion sizes and longer PRL-fovea distances, both of which were strongly correlated with worse BCVA. This suggests that the reduced visual acuity in younger patients is not solely age-related, but is mediated by greater anatomical disruption of the central retina and less efficient fixation adaptation. As expected, increased lesion size and PRL-fovea distance were associated with decreased visual acuity, confirming that retinal sensitivity decreases with increasing distance from the fovea, as previously reported in studies of eccentric PRLs in both JMD and AMD patients.^{7,11,19,27}

Our finding that superiorly located PRLs were more common in older patients suggests that cortical adaptation mechanisms contribute to PRL development and optimization over time. This interpretation is supported by evidence that visual cortical networks reorganize in response to altered input, even beyond the critical period of visual development. Cheung and Legge¹³ demonstrated that patients with central vision loss engage both perceptual and oculomotor recalibration processes, enabling the emergence of more functionally advantageous PRLs. More recently, Kolawole et al.²⁸ used high-resolution imaging to show that eccentric PRLs are not merely anatomically determined, but represent functionally optimized loci shaped by higher-order cortical processing. These findings provide a neurofunctional basis for the age-related PRL relocation we observed in JMD patients.

From a rehabilitation perspective, PRL location has substantial clinical implications. Spontaneously developed PRLs may be suboptimal (e.g., unstable, located far from the fovea, or positioned in areas with reduced retinal sensitivity), necessitating specific interventions. Eccentric viewing training facilitates the use of more effective peripheral retinal loci for visual tasks and has long been a cornerstone of functional rehabilitation in patients with central vision loss. Early studies emphasized the importance of behavioral training in stabilizing PRL usage and improving visual performance.^{23,29,30}

More recently, targeted training approaches combining perceptual and oculomotor exercises have been shown to accelerate the establishment of a stable pseudofovea,²⁴ shedding light on the underlying neuroplastic mechanisms that contribute to PRL optimization in conditions like JMD.³¹ In line with these advancements, microperimetry-based acoustic biofeedback training has also been shown to enhance PRL stability and reading performance in patients with central scotoma.³² In addition, optical strategies such as prism relocation may help shift fixation toward more functionally advantageous loci. Incorporating these approaches into low-vision rehabilitation programs for JMD could improve both distance and near vision performance.

Study Limitations

This study has several limitations. First, as a retrospective study with a modest sample size, our findings should be interpreted with caution and validated in larger, prospective cohorts. Second, all measurements were obtained monocularly. In real-life viewing conditions, binocular interactions and dominance effects can influence PRL characteristics and may yield different functional outcomes. Third, we did not assess retinal sensitivity values in decibels, which would have provided additional information about the functional capacity of the eccentric fixation areas. Fourth, our analysis did not include near-vision performance parameters such as reading acuity, critical print size, maximum reading speed, and reading ease. These measures are particularly relevant for evaluating the everyday functional implications of PRL location and stability.

Future studies should therefore aim to incorporate binocular assessments, detailed retinal sensitivity mapping, and standardized continuous-text reading tests in addition to traditional visual acuity outcomes. Such a comprehensive evaluation would provide a more complete understanding of PRL adaptation and its clinical significance in JMD.

Conclusion

This study demonstrates that in JMD, PRLs are most often positioned superiorly or nasally, and their location is significantly correlated with patient age. Younger patients tend to exhibit nasally located PRLs that lie farther from the fovea, a pattern associated with larger lesion sizes, greater PRL-fovea distances, and consequently poorer visual acuity. In contrast, older patients more commonly show superior PRLs, which are functionally advantageous for tasks such

as reading and mobility. These findings support the role of cortical adaptation mechanisms in the age-related relocation and optimization of PRLs, underscoring the potential benefit of harnessing or guiding this adaptation in clinical practice. From a rehabilitation standpoint, when spontaneous PRLs are unstable or suboptimally located, targeted interventions such as eccentric viewing training, combined perceptual-oculomotor protocols, and optical strategies like prism relocation should be considered to promote the development of a stable and effective pseudofovea. Although near-vision parameters were not assessed in this retrospective study, future work should integrate reading performance measures to better capture the functional implications of PRL characteristics in daily life. In summary, recognizing the distinct PRL patterns and their relationship with age, lesion size, and visual function in JMD is essential for designing individualized, evidence-based low-vision rehabilitation strategies that optimize visual outcomes in this young patient population.

Ethics

Ethics Committee Approval: The study protocol adhered to the tenets of the Declaration of Helsinki, with approval obtained from the Ethics Committee of Dokuz Eylül University (date: 23.06.2021, approval number: 2021/19-22 [6371-GOA]).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.E., Concept: M.E., Z.Ö.T., T.Ö., Design: M.E., Z.Ö.T., T.Ö., Data Collection or Processing: M.E., Z.Ö.T., T.Ö., Analysis or Interpretation: M.E., Z.Ö.T., T.Ö., Literature Search: M.E., Z.Ö.T., T.Ö., Writing: M.E., Z.Ö.T.

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Evaluating the Predictive Accuracy of the Kane and SRK/T Formulas in Keratoconus Patients Undergoing Cataract Surgery

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Abstract

Objectives: To compare the predictive performance of the SRK/T and Kane formulas in eyes with keratoconus undergoing cataract surgery.

Materials and Methods: A consecutive series of keratoconic eyes that underwent cataract surgery were retrospectively analyzed. Intraocular lens power was calculated using the SRK/T and Kane Keratoconus formulas. Subjective refraction was evaluated 1 month postoperatively. The mean prediction error (MPE) and percentage of eyes with a prediction error within ± 0.50 diopters (D) and ± 1.00 D were calculated. Patients were divided into two categories: early-stage (stage 1) and advanced-stage (stage 2-3) keratoconus.

Results: Thirty eyes of 25 patients were included in the study. A comparison of MPE between the two formulas in the stage 1 keratoconus group revealed no statistical difference. However, the MPE for the SRK/T formula was found to be significantly higher ($p=0.005$) in the stage 2-3 group. In the stage 1 group, 84.6% of eyes were within the PE range of ± 1.00 D based on the Kane formula, while 76.9% of eyes fell within the ± 1.00 D range according to the SRK/T formula. In stage 2-3 group, 41.2% of eyes were within the PE range of ± 1.00 D based on the Kane formula, while 29.4% of eyes fell within the ± 1.00 D range according to the SRK/T formula.

Conclusion: A comparison of the two formulas showed no statistically significant differences in early-stage keratoconus. However, in advanced keratoconus cases, the Kane formula exhibited superior accuracy.

Keywords: Cataract surgery, Kane formula, keratoconus, optical biometry, SRK/T formula

Introduction

Keratoconus is a progressive corneal disorder that manifests with thinning of the cornea and the formation of a cone-shaped protrusion, resulting in a deterioration of visual acuity.¹ While early-stage management options (such as contact lenses and corneal cross-linking) can be effective in stabilizing the condition, advanced cases may require surgical intervention, including corneal transplantation.² Cataract formation also becomes increasingly common with age in patients with keratoconus, but performing cataract surgery in these individuals presents a significant challenge due to the difficulty in accurately predicting refractive outcomes.^{3,4}

The efficacy of cataract surgery is contingent on the selection of an appropriate intraocular lens (IOL). However, corneal irregularities and limitations in biometric measurements in keratoconic eyes create significant challenges in this process.^{5,6} Accordingly, selecting the most appropriate biometric formula is crucial to achieving optimal refractive results after cataract surgery on keratoconic eyes. Several formulas are commonly used for IOL power calculations, including SRK/T, Holladay, Haigis, and Kane.⁷ While the SRK/T formula is widely utilized, particularly in longer eyes, hyperopic deviations have been noted in eyes with keratoconus.⁸ The Kane formula is a more recent advancement reported to provide superior accuracy in cases with irregular corneal morphology.⁹

The purpose of this study was to evaluate the refractive outcomes of cataract surgery in eyes with keratoconus and to compare the performances of the SRK/T and Kane formulas in IOL power calculation. There remains limited comparative data on these formulas in advanced keratoconus. The present study

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Preliminary results of this study were presented as an oral presentation at the 58th TOA National Congress (November 20-24, 2024).

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aims to address this literature gap and thereby provide clinicians with guidance to improve the refractive success rate of cataract surgery in patients with keratoconus.

Materials and Methods

A retrospective analysis was performed with consecutive keratoconus patients who underwent cataract surgery at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital between January 2022 and December 2024. Patients were included if corneal specialists diagnosed them with keratoconus based on corneal tomography findings (Sirius+, C.S.O., Florence, Italy). The exclusion criteria comprised a prior history of intraocular surgery, corneal scarring, intraoperative or postoperative complications, and postoperative spectacle-corrected visual acuity below 20/40. The study received approval from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (protocol code: 2025-32, decision no: 32, date: 29.01.2025), and all participants provided written informed consent in compliance with the ethical principles outlined in the Helsinki Declaration.

A subsequent analysis was conducted to categorize patients based on keratoconus severity, according to the classification criteria defined by Krumeich et al.¹⁰ Eyes were designated as stage 1 if their maximum keratometry was less than or equal to 48 diopters (D), stage 2 if it ranged between 48 D and 53 D, and stage 3 if it exceeded 53 D. Because of the limited number of cases, patients with stage 2 and stage 3 keratoconus were combined and analyzed as a single group. For further evaluation, patients were classified as early stage (stage 1) and advanced stage (stages 2 and 3).

All patients underwent preoperative IOL power calculations using the same optical biometer (OA-2000, Tomey Corporation, Nagoya, Japan). In all cases, IOL power was selected as the closest myopic value to emmetropia according to the SRK/T formula. Standard phacoemulsification surgery with a temporal main incision was performed by experienced surgeons, and all patients received a one-piece hydrophobic acrylic IOL (Enova, VSY Biotechnology, Leinfelden-Echterdingen, Germany) with no additional astigmatism-correcting procedures performed. Postoperatively, all patients were treated with topical steroids and antibiotics.

Optical biometry was utilized to calculate the SRK/T formula, while the Kane keratoconus formula was computed using the Kane online calculator (<https://www.iolformula.com>). In both formulas, the IOL power was selected as the nearest myopic value to emmetropia. Prediction errors were calculated by subtracting the expected postoperative refraction from the spherical equivalent measured 1 month after surgery. For each formula, the mean absolute prediction error (MAPE), the mean prediction error (MPE), the median absolute prediction error, and the standard deviation of prediction error were determined. Furthermore, the percentage of eyes with prediction errors within ± 0.50 D and ± 1.00 D was assessed for each formula.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed using the Kolmogorov-Smirnov test and histogram analysis. Descriptive data were presented as mean $\pm$ standard deviation. Differences between dependent variables were analyzed using the Wilcoxon rank test. A p value of less than 0.05 was considered statistically significant.

Results

The study included a total of 30 eyes from 25 patients. The mean age was 61.2 ± 11.4 years (range, 39 to 82) and 17 (68%) patients were female. The mean postoperative spherical equivalent was -0.79 ± 1.70 D (range, -6.25 to +3.25). In accordance with the modified Krumeich classification scheme, 13 eyes were categorized as stage 1 and 17 eyes were classified as stage 2 or 3. The demographics of the study cohort are presented in [Table 1](#).

The mean values for the selected IOLs according to the Kane formula and the SRK/T formula were 20.45 ± 2.21 D (range, 16.50 to 24.00) and 20.21 ± 2.24 D (range, 16.50 to 23.50) in stage 1 eyes and 18.50 ± 4.70 D (range, 11.50 to 26.00) and 17.61 ± 5.00 D (range, 9.00 to 25.00) in stage 2-3 eyes, respectively. In stage 1 keratoconus, no significant difference was observed between the SRK/T and Kane formulas with respect to mean IOL power. However, in stage 2-3 keratoconus, the mean IOL power selected according to the SRK/T formula was significantly lower ($p=0.007$).

The prediction error for each group is displayed in [Table 2](#). In the stage 1 keratoconus group, the MPE and MAPE were comparable across the two formulas. An analysis of the stage 2-3 keratoconus group revealed a hyperopic shift when using the SRK/T formula. The MPE was found to be more

Table 1. Demographic and ocular data of the patients according to keratoconus stage

	Stage 1 (n=13)	Stage 2-3 (n=17)
Age (years)	63.8 ± 12.3 (39 to 78)	59.2 ± 10.7 (46 to 82)
Gender (female), n (%)	9 (69.2)	11 (64.7)
Postoperative SE (D)	-0.38 ± 1.47 (-2.75 to +1.25)	-1.12 ± 1.85 (-6.25 to +3.25)
K1 (D)	42.81 ± 1.51 (40.23 to 45.07)	46.40 ± 2.15 (42.59 to 57.76)
K2 (D)	45.39 ± 1.40 (41.53 to 47.83)	49.36 ± 3.33 (44.71 to 59.31)
ACD (mm)	3.29 ± 0.44 (2.67 to 4.04)	3.26 ± 0.55 (2.74 to 4.21)
Axial length (mm)	23.63 ± 0.56 (21.89 to 26.59)	22.63 ± 1.30 (21.65 to 28.81)

D: Diopters, SE: Spherical equivalent, K1: Flat keratometry value, K2: Steep keratometry value, ACD: Anterior chamber depth

hyperopic with the SRK/T formula compared to the Kane formula ($p=0.005$). However, the MAPE was comparable across the two formulas in stage 2-3 keratoconus. Among all cases, 12 eyes (40%) fell within the prediction error range of ± 0.50 D based on the Kane formula, while 9 eyes (30%) fell within the ± 0.50 D range based on the SRK/T formula. For the error range of ± 1.00 D, these values were 18 eyes (60%) and 15 eyes (50%), respectively. The rates of prediction error within ± 0.50 D and ± 1.00 D according to keratoconus stage are presented in Table 3.

Discussion

The IOL power calculation process is considerably less accurate in eyes with keratoconus than in normal eyes, and most existing formulas typically lead to hyperopic refractive results in these patients.^{3,11,12,13,14,15} In this study, we compared the SRK/T formula, an older formula that has been reported as yielding favorable outcomes in keratoconus cases, with the newer Kane formula, which has also shown superior results in patients with keratoconus.^{9,11,12}

Previous studies have indicated that of the conventional formulas, the SRK/T formula demonstrates the highest accuracy in keratoconic eyes, with MPE and MAPE ranging from $+0.22$ to $+0.91$ D and from 0.47 to 1.00 D, respectively.^{3,11,12} Recent studies have documented that the MPE and the MAPE of the Kane formula range from -0.28 D to $+0.22$ D and from 0.49 D to 0.92 D, respectively.^{9,15,16} In a study by Kane et al.⁹, the MPE in eyes with stage 1 keratoconus was found to be -0.18 D and -0.23 D with the Kane and SRK/T formulas, respectively. In stages 2 and 3 keratoconus respectively, MPEs were 0.53

and 0.02 according to the Kane formula.⁹ Consistent with their findings, our stage 2-3 group also had MPE values within this range. Using the SRK-T formula, Kane et al.⁹ reported MPE values of 0.51 and 1.86 in the stage 2 and stage 3 keratoconus groups, respectively. In the present study, the MPE for the stage 2-3 group was 0.79 , again aligning with earlier established values.

In a study by Yokogawa et al.¹⁶, the Kane formula resulted in greater hyperopic outcomes in the stage 1 group, with a MPE of $+0.68 \pm 0.87$ D; in contrast, the SRK/T formula demonstrated a closer alignment with emmetropia in the same group, yielding an MPE of $+0.23 \pm 1.18$ D. One potential explanation for this finding is that the mean keratometry values of the patient cohort were slightly higher, as acknowledged in the article. Furthermore, after comprehensive evaluation of all cases in the study, the authors reported that the Kane formula yielded more successful results than the SRK/T formula.¹⁶

The superior performance of the SRK/T formula in keratoconus cases relative to other older-generation formulas is hypothesized to result from its tendency to overestimate IOL power in steep corneas, as evidenced in the study by Melles et al.¹⁷ This overestimation is believed to compensate for the hyperopic shift observed in most formulas in keratoconus patients.¹² In this context, the Kane keratoconus formula utilizes a modified corneal power that is based on the anterior corneal radius of curvature, offering a more accurate representation of the anterior/posterior ratio in eyes affected by keratoconus.⁹ Additionally, it reduces the impact of corneal power on the effective lens position calculation, leading to more precise estimates.

Study Limitations

The most significant limitation of our study is the single-center design and relatively small sample compared to those in the multicenter studies that dominate the literature on IOL calculations for patients with keratoconus. In addition, due to the limited number of patients with either stage 2 or stage 3 keratoconus, these cases were assessed collectively in this study. Furthermore, although the follow-up period lasted at least 1 month and the surgery was performed on patients with stable keratoconus, refractive stability may continue to improve for up to 6 months postoperatively, particularly in eyes with thin corneas affected by keratoconus.¹⁸

However, this study is distinct from multicenter studies in its use of a singular optical biometer and IOL across all patients, a feature that contributes to its methodological strength.

Conclusion

In the early stages of keratoconus, no significant differences were observed between the Kane and SRK/T formulas, and residual refraction showed comparable characteristics. In advanced stages of keratoconus, the Kane formula demonstrated significant alignment toward emmetropia, whereas the SRK/T formula tended to induce a hyperopic shift. It is imperative that future prospective studies include greater numbers of participants and patients with severe keratoconus in particular,

Table 2. The prediction error of the two formulas according to keratoconus stage

Formula	MAPE	MPE	STDEV	MedAPE
Stage 1				
Kane (D)	0.86	-0.04	1.20	0.55
SRK/T (D)	1.00	0.14	1.32	0.75
Stage 2-3				
Kane (D)	1.32	0.24	1.73	1.12
SRK/T (D)	1.51	0.79	1.67	1.27

D: Diopters, MAPE: Mean absolute prediction error, MPE: Mean prediction error, STDEV: Standard deviation of the prediction error, MedAPE: Median absolute prediction error

Table 3. Percentages of eyes with prediction error within ± 0.50 and ± 1.00 D according to keratoconus stage

	Stage 1 (n=13)		Stage 2-3 (n=17)	
	± 0.50 D	± 1.00 D	± 0.50 D	± 1.00 D
Kane	53.8%	84.6%	29.4%	41.2%
SRK/T	46.2%	76.9%	17.6%	29.4%
p value	1.000	1.000	0.688	0.720

D: Diopters

so as to more accurately assess the predictive capabilities of the formulas in these challenging cases.

Ethics

Ethics Committee Approval: The study received approval from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (protocol code: 2025-32, decision no: 32, date: 29.01.2025).

Informed Consent: All participants provided written informed consent in compliance with the ethical principles outlined in the Helsinki Declaration.

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Declarations

Authorship Contributions

Surgical and Medical Practices: Y.B.A., F.O.A., A.C., Y.Y., Concept: Y.B.A., B.K.Y., A.C., Design: Y.B.A., H.D., B.K.Y., Data Collection or Processing: H.D., F.O.A., Analysis or Interpretation: B.K.Y., Y.Y., F.O.A., Literature Search: Y.B.A., A.C., Y.Y., H.D., Writing: Y.B.A., H.D., F.O.A., A.C., B.K.Y., Y.Y.

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Optimizing Perioperative Management Strategies in Uveitic Cataract Surgery: A Survey of Expert Practices

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Abstract

Objectives: To evaluate the current practices in uveitic cataract surgery based on expert opinions and identify areas of agreement and divergence.

Materials and Methods: A descriptive, cross-sectional expert survey was conducted among tertiary referral centers and university hospitals in Türkiye. A structured 10-item questionnaire was electronically distributed to uveitis specialists who had at least 5 years of experience in uveitis, were in active clinical practice, and managed at least 50 uveitic cataract cases per year. The questionnaire addressed preoperative preparation, intraoperative approach, and postoperative management. Multiple answers were permitted. Descriptive statistics were used for analysis. The terms “strong consensus”, “consensus”, and “divergence” were used to categorize levels of agreement.

Results: Strong consensus was observed for a 3-month inflammation-free period before surgery (85%, 17/20), continuation of conventional immunosuppressants without dose adjustment (95%, 19/20), and preference for hydrophobic acrylic intraocular lenses in uveitis associated with juvenile idiopathic arthritis (80%, 16/20). In postoperative management, 80% (16/20) tapered topical steroids within 4-6 weeks. For biologic therapies, 75% (15/20) adjusted surgical timing based on pharmacodynamic half-life. Preoperative topical steroid strategies showed divergence, with no dominant protocol. Steroid coverage strategies were practiced differentially; 65% (13/20) relied on topical steroids alone in anterior uveitis, while 60% (12/20) used intravenous steroids for posterior/panuveitis. Non-steroidal anti-inflammatory drug use for macular edema

prophylaxis varied widely, and recurrence management involved systemic steroids (70%, 14/20), periocular injections (55%, 11/20), or intravitreal therapy (40%, 8/20).

Conclusion: Expert consensus highlights standardized perioperative strategies in uveitic cataract care. However, considerable variation persists in several key areas, emphasizing the need for further research. Personalized approaches remain crucial.

Keywords: Expert survey, inflammation-free period, macular edema prophylaxis, perioperative management, uveitic cataract surgery

Introduction

Cataract is a frequent and vision-threatening complication of uveitis, resulting from chronic/recurrent intraocular inflammation and prolonged corticosteroid exposure.^{1,2} In uveitic patients, cataract impairs visual acuity and limits the clinician's ability to evaluate the posterior segment, thereby complicating imaging and therapeutic monitoring.³

Technological advancements in cataract surgery and improved perioperative control of inflammation have made uveitic cataract surgery increasingly safe and successful. Nevertheless, perioperative management poses a series of unique challenges due to the need for aggressive control of inflammation while minimizing treatment-related complications. Especially in patients receiving systemic immunosuppressants or biological agents, surgical timing and perioperative immunomodulatory strategies require a careful balance, with adequate suppression to prevent intraocular inflammation but awareness of the increased risks of infection and delayed tissue healing.^{1,4} The attainment of a favorable outcome is based on thorough preoperative management, individualized approaches tailored to the patient, a precise and uncomplicated surgery, and postoperative control of complications.^{4,5}

Cataract surgery in uveitis requires an individualized approach. The heterogeneity of uveitic entities and ongoing medical treatments and the varying severity of inflammation and

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other associated ocular and systemic factors make it difficult to establish a universal strategy. While general recommendations exist, there is no globally accepted guideline for perioperative management. In daily practice, management depends on individual patient characteristics and clinician experience.^{1,4,5,6} Given the relatively small number of ophthalmologists specializing in uveitis, expert opinion is particularly valuable in defining best practices for this patient group.

This study aimed to evaluate the real-world clinical decision-making process regarding perioperative management strategies for uveitic cataract surgery in Türkiye, focusing on preoperative, intraoperative, and postoperative practices. Identifying areas of consensus and divergence is expected to contribute to a deeper understanding of the factors influencing surgical planning and postoperative management.

Materials and Methods

This descriptive, cross-sectional study was conducted with experienced ophthalmologists managing uveitic patients in Türkiye to evaluate real-life perioperative management practices in uveitic cataract surgery. Ethical approval was not required and the study complied with the tenets of the Declaration of Helsinki.

The questionnaire was administered in Turkish to ensure clarity and accessibility and consisted of 10 multiple-choice questions carefully designed to assess different aspects of perioperative management. Questions 1-6 addressed preoperative management, question 7 focused on intraocular lens (IOL) preferences, and questions 8-10 covered postoperative strategies. The complete questionnaire is available as [Supplementary Material 1](#). The questionnaire was reviewed and validated by two uvea specialists (C.A. and B.Y.O.) to ensure content relevance and clarity.

Participants were selected based on the criteria of having at least 5 years of experience in uveitis management, being actively engaged in clinical practice in Türkiye, and performing at least 50 uveitic cataract surgeries per year. All respondents were certified specialists, predominantly working in tertiary referral hospitals or university clinics.

The survey was administered electronically via the SurveyMonkey electronic platform and distributed through electronic communication channels, including professional networks and targeted email invitations. To reflect the diversity of real-world practices, participants were allowed to select multiple answers for each question.

Responses were collected anonymously over a defined period (February 1-28, 2025). No personal or institutional identifiers were obtained, and participation was voluntary.

Statistical Analysis

The survey responses were compiled and analyzed using Microsoft Excel and SPSS for Mac version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize response frequencies and percentages for each question. Based on response rates, areas of consensus and divergence were identified

to highlight patterns of practice in perioperative management ([Table 1](#)).

Results

The study questionnaire was distributed to 25 uveitis specialists meeting the selection criteria and was completed by 20 of them (80% return rate).

The distribution of responses to questions 1-6 regarding preoperative management along with their respective percentages are presented in [Table 2](#).

Table 1. Consensus definitions used in the study

Classification	Definition
Strong consensus	≥75% of participants selected the same response AND ≥20% difference from the next best option
Consensus	60-74% of participants selected the same response AND ≥15% between the two most selected answers
Divergence	Either 50-59% selected the same response OR <15% difference between the two most selected answers

Table 2. Preoperative strategies and response distribution

Question	Option	% (n)
Q1. Preoperative inflammation-free period	3 months	85% (17)
	6 months	15% (3)
	Patient-dependent	15% (3)
Q2. Preoperative topical steroids	1-3 days before, 3-5 drops/day	35% (7)
	1-3 weeks before, 3-5 drops/day	30% (6)
	Not used	35% (7)
	1-3 days before, hourly	20% (4)
	1-3 weeks before, hourly	30% (6)
Q3. Steroid coverage (anterior uveitis)	Topical only	65% (13)
	IV steroid on surgery day	10% (2)
	Increase preop systemic dose	20% (4)
	Add systemic postop	10% (2)
	Not applied	30% (6)
Q4. Steroid coverage (posterior/panuveitis)	IV steroid on surgery day	60% (12)
	Increase preop systemic dose	40% (8)
	Add systemic postop	25% (5)
	Topical only	10% (2)
	Not applied	15% (3)
Q5. Conventional IST before surgery	Continue without change	95% (19)
	Increase dose	5% (1)
Q6. Biologic agent management	Time surgery to half-life	75% (15)
	Do not interrupt	45% (9)
	Skip one dose	15% (3)

IST: Immunosuppressive therapy, IV: Intravenous, Q: Question, n: Number of responses of participants. The option with the highest rate of selection is marked in bold

The survey included only a single question concerning intraoperative management. This question focused on IOL selection in patients with juvenile idiopathic arthritis (JIA)-associated uveitis. The respondents preferred the implantation of a hydrophobic acrylic IOL (80%, 16/20). A smaller proportion of specialists preferred deferring IOL implantation to a second session (20%, 4/20), while only 10% (2/20) reported using hydrophilic lenses.

The distribution of the responses to questions 8-10, which focused on postoperative anti-inflammatory strategies, are shown in [Table 3](#).

[Table 4](#) summarizes the survey results based on the predefined classification criteria for consensus and divergence.

Discussion

Uveitic cataract surgery represents a highly complex intersection of cataract and inflammatory disease management, challenging even the most experienced surgeons. Unlike senile

cataracts, the perioperative management of uveitic cataracts is highly individualized. The management is dependent on the underlying etiology of uveitis, anatomical complications, and the systemic immunosuppressive therapy (IST) received by the patient.⁷ The current guidelines provide limited specific recommendations, leaving the majority of decisions to the discretion of the managing clinician. In this context, the present survey-based study provides valuable insight into real-world clinical preferences and highlights areas of consensus among ophthalmologists experienced in uveitic cataract. These findings aimed to provide a basis for future controlled studies on areas of divergence.

Question 1 focused on the inflammation-free period before surgery. According to the survey results, 85% of the experts recommended a 3-month quiescent period. This finding is broadly consistent with the common view in the literature. Numerous studies have emphasized the importance of quiescence of inflammation for a period of at least 3 months prior to cataract surgery.^{5,7,8,9,10} It is hypothesized that this period is conducive to a reduction in postoperative complications, particularly cystoid macular edema (CME).^{9,11} In an expert survey conducted by International Uveitis Study Group (IUSG), 70% of respondents preferred 3 months, while 11% indicated a tendency to wait longer (e.g., 6 months).¹² In a study conducted on pediatric uveitis patients, the shortest inflammation-free period was reported to be 6 months, and this was found to be safe.¹³ However, some studies suggest that surgery may be considered in patients with recurrent or chronic uveitis during a “window of opportunity” when inflammation is better controlled.¹⁴ The etiology of uveitis is also a significant factor in this decision-making process. Patients diagnosed with Fuchs uveitic syndrome were reported to have a favorable prognosis following cataract surgery, even when the anterior chamber reaction is not fully controlled.¹⁵ A study on the outcomes of cataract surgery in patients diagnosed with Vogt-Koyanagi-Harada disease found no significant difference in postoperative outcomes between a 1-month or 3-month inflammation-free period before surgery.¹⁶ Although the literature on this subject is based primarily on expert opinion, a recent study showed that longer quiescence periods, such as 30, 60 or 90 days, significantly reduced the risk of recurrence within the first 90 days.¹⁰

Question	Option	% (n)
Q8. Tapering topical steroids	4-6 weeks	80% (16)
	3 months	35% (7)
	6 months	5% (1)
Q9. NSAID for CME prophylaxis	Postop only (1 month)	45% (9)
	Not used	35% (7)
	1 week preop	20% (4)
	1-3 days preop	5% (1)
Q10. Postop recurrence management	Add systemic steroid	70% (14)
	Periocular steroid	55% (11)
	Intravitreal steroid	40% (8)
	Increase topical + add systemic	35% (7)
	Increase IS dose	20% (4)
	Add new IS agent	15% (3)
	Increase topical only	5% (1)

CME: Cystoid macular edema, NSAID: Non-steroidal anti-inflammatory drug, Preop: Preoperative, Postop: Postoperative, IS: Immunosuppressive, Q: Question, n: number of responses from participants. The option with the highest rate of selection is marked in bold

Strong consensus	Consensus	Divergence
Q1: 3-month inflammation-free period preoperatively (85%)	Q3: Topical-only for anterior uveitis (65%)	Q2: Preoperative topical steroid regimens (mixed)
Q5: Continue conventional IST unchanged (95%)	Q4: IV steroid on surgery day for posterior/panuveitis (60%)	Q9: NSAID use for CME prophylaxis (varied approaches)
Q7: Hydrophobic acrylic IOL for JIA (80%)	Q6: Time surgery with biologic half-life (75%)	Q10: Postop recurrence strategies (no dominant choice)
Q8: Taper topical steroids in 4-6 weeks (80%)		

*Strong consensus was defined as ≥75% agreement with at least a 20% margin from the next response, consensus was defined as 60-74% agreement with a 15% margin, and responses without a clear majority or with <15% margin were considered divergent
CME: Cystoid macular edema, IOL: Intraocular lens, IST: Immunosuppressive therapy, IV: Intravenous, JIA: Juvenile idiopathic arthritis, NSAID: Non-steroidal anti-inflammatory drug, Q: Question

Question 2 focused on preoperative topical steroid regimen preferences. The responses demonstrated significant variability, with no dominant protocol emerging. This finding aligns with recent observations in the literature.^{8,17} While the administration of topical steroids prior to surgery is common practice, there is no standardized protocol concerning dosage, frequency, or duration.¹⁴ Different regimens have been described in previous studies, including every hour on the day before, 8 to 12 times a day for 2 days before, 4 times daily for 72 hours before, and 3, 4, 5, or 6 times a day for 1 week before surgery.^{1,4,5,18,19,20,21,22,23} This diversity is reflected in the distribution of survey results and the variation in practice. The current literature lacks clear, high-level evidence-based guidance on this topic.¹²

Question 3 addressed the use of steroid coverage strategies for the management of anterior uveitis. A moderate consensus emerged, with 65% of experts preferring management with topical steroids alone in patients with anterior uveitis. This finding aligns with the established principle that preoperative regimens should be adapted according to the anatomical classification of uveitis and the severity of disease.⁸ Some reports suggest that topical steroid use alone may be sufficient in patients with inactive isolated anterior uveitis or where inflammation is controlled with topical treatment alone, as stated above.^{1,8,17} Conversely, in more complex or severe cases (posterior/panuveitis, persistent inflammation, high-risk patients), the necessity of systemic steroids or other immunosuppressives is emphasized.^{5,8} The 30% of participants who reported not using a preoperative steroid coverage strategy may be indicative of the view that in very mild or single-episode cases, no additional steroid protection is required.

Question 4 addressed steroid coverage strategies in cases of posterior/panuveitis. The survey results indicated that 60% of the experts favored the administration of intravenous (IV) steroids on the day of surgery, 40% preferred preoperative systemic dose escalation, 25% preferred postoperative systemic supplementation, 10% preferred topical treatment alone, and 15% used no additional treatment. As stated in the discussion of question 3, the type and severity of uveitis are crucial factors, and more intensive preoperative steroid prophylaxis may be necessary in high-risk uveitis cases with severe inflammation, such as panuveitis, or those prone to aggressive postoperative inflammation.^{5,8} Various protocols have been proposed in the literature: 1 g IV methylprednisolone daily for 3 days prior to surgery, a single dose of IV methylprednisolone (15 mg/kg) half an hour before surgery, or oral prednisolone (0.5-1 mg/kg/day) started up to 2 weeks prior to surgery and then tapered.^{5,8,9,18,22,24} In one study, a 2-week preoperative course of oral prednisolone was found to be more efficacious in recovering blood aqueous barrier function than a single dose of IV methylprednisolone.²⁵ The IUSG expert survey similarly demonstrated that preoperative systemic corticosteroid escalation is common (76%), but there is variation in dosage and timing.¹² Considering this variation, the 60% consensus in the present study suggests that the indicated IV regimen is a common preference, though there are

alternative approaches in the literature that are considered valid or equivalent.

Question 5 assessed views on adjusting conventional IST preoperatively. The survey revealed a strong consensus among experts, with 95% expressing their agreement that conventional IST should be maintained without any alteration in dosage. This result is consistent with the literature, which states that uveitic patients who are scheduled to undergo cataract surgery, particularly those exhibiting no inflammatory activity, should continue their current maintenance immunosuppressive regimen.^{5,8}

Question 6 addressed the management of perioperative biologic agents. The majority of experts (75%) preferred to adjust the timing of surgery according to half-life, with 45% stating they did not interrupt treatment and 15% preferring to skip a dose. Biological agents are used in cases of severe or refractory uveitis.^{5,24} The most critical prerequisite for cataract surgery is the quiescence of inflammation, and biological agents are a part of this suppression.^{9,22} There is an absence of detailed protocols in the literature regarding the adjustment of surgical timing according to the specific half-life of biological agents. Nonetheless, expert opinion suggests that pharmacokinetic profiles are considered during surgical planning. The objective is presumably to identify the window in which the biological agent's efficacy is at its zenith, during which the probability of surgical stress-induced inflammation is lower. The 45% preference for not interrupting treatment is consistent with the general principle of maintaining systemic immunomodulation to reduce the risk of flare.^{5,8} Our findings point to the increasing role of biological agents in uveitis management and a more sophisticated surgical decision-making process based on their properties.

Question 7 addressed IOL preferences in JIA-associated uveitis, a subgroup with a high risk of postoperative complications.² In the present survey, 80% of respondents reported a preference for hydrophobic acrylic IOLs, while 20% opted to defer IOL implantation and 10% preferred hydrophilic IOLs. IOL implantation in JIA cases has historically been the subject of controversy, with aphakia frequently being favoured.^{1,5,21} Nevertheless, contemporary approaches indicate that IOL implantation in this group can be both feasible and successful when perioperative inflammation is stringently controlled.^{13,21,26} In a study focusing on JIA-associated uveitic cataract, favorable visual outcomes were reported in patients who were quiescent for a period of at least 6 months preoperatively.¹³ Comparative studies on IOL materials have generally focused on uveitic eyes as a whole rather than specifically on JIA. The existing literature consistently demonstrates that acrylic lenses are associated with lower rates of inflammation, posterior capsular opacification, and CME compared to materials such as silicone or poly(methyl methacrylate), thus supporting their superior biocompatibility.^{18,27} Direct comparisons have been made between hydrophobic and hydrophilic acrylic lenses, with hydrophilic IOLs demonstrating slightly higher flare and CME rates.

However, other studies have indicated that modern hydrophilic acrylic lenses possess satisfactory uveal biocompatibility.^{23,28} These findings help explain the predominant preference for hydrophobic acrylic IOLs in the current survey. Our results are consistent with those of the IUSG survey, in which 71% of responders preferred hydrophobic acrylic IOLs.¹² The authors emphasized that IOL selection in such complex cases is largely guided by individual clinical experience, reflecting the perceived absence of high-level evidence.¹² In brief, the current survey data indicate that when inflammation is adequately controlled, IOL implantation is widely favored in JIA-associated uveitis, with hydrophobic acrylic lenses being the dominant choice among experienced clinicians.

Question 8 asked about approaches to tapering topical corticosteroids in the postoperative period of uncomplicated cataract surgery. A strong consensus was observed, with 80% of participants favoring a 4-6 week tapering period. The literature highlights the significance of regulating postoperative inflammation following cataract surgery in uveitic eyes. The severity of postoperative inflammation determines the frequency of topical steroid use.^{4,5,19,20,21} The taper times of topical steroids may vary in the literature.^{19,29} In this context, the 4-6 week period in this survey may be consistent with shorter or intermediate taper regimens. However, in severe or persistent cases, the use of topical steroids over a longer period (3-4 months or 6 months) may also be indicated.^{6,19,28}

Question 9 assessed the use of non-steroidal anti-inflammatory drug (NSAID) drops for CME prophylaxis in the postoperative period. Topical NSAID drops were utilized by 60% (12/20) of the participants, with considerable variability in timing and duration. Topical NSAID drops play a pivotal role in the prevention of CME.³⁰ According to the literature, combination therapy (topical steroids + NSAIDs) appears more effective than steroids alone in reducing CME risk in severe uveitis.^{31,32,33} A study focusing on postoperative NSAID use in Behçet's uveitis reported reduced inflammation, although CME outcomes were not specifically assessed.³⁴ In alignment with current reviews, our results confirm that NSAIDs are frequently incorporated as adjunctive agents rather than replacements for steroids. However, the lack of uniformity in practice patterns suggests a need for further evidence-based guidance, particularly regarding timing, duration, and indications tailored to disease severity.

The responses to question 10, regarding the preferred treatment approaches in immunosuppressed patients with posterior/panuveitis recurrence in the postoperative period, demonstrate a high level of agreement with extant literature. The majority of the experts preferred systemic steroid administration (70%) as first-line treatment, followed by periocular (55%) and intravitreal (40%) steroid administration. High-dose oral or IV corticosteroids remain the cornerstone for managing severe flare-ups.^{1,5,6,7,8,11,21,24,25} In severe exacerbations, IV methylprednisolone or high-dose oral corticosteroids have been recommended.^{9,25} In several studies, periocular steroid administration has been emphasized as a potential alternative to systemic steroids.³⁵ Intravitreal triamcinolone and dexamethasone implants

were also shown to be effective in controlling postoperative inflammation and providing targeted therapy with reduced systemic side effects.^{5,24} It has been hypothesized that intravitreal triamcinolone may be more efficacious than orbital floor triamcinolone with regard to CME and early inflammation.²⁰ A comparative study conducted between systemic steroids and intravitreal administration revealed comparable outcomes in terms of postoperative inflammation control and visual recovery. However, intravitreal use was associated with an increase in intraocular pressure, while systemic administration was linked to the development of CME.¹⁹ An alternative approach, which was less frequently favored in our study but has a place in the literature, involves increasing the dose of existing IST (20%) or adding a new agent (15%). It has been documented that these options are being considered in cases resistant to steroid treatment or those with frequent recurrences.^{4,21} In light of these data, the survey results suggest that multiple routes of steroid administration are commonly used in practice for the management of recurrence after uveitic cataract surgery, but patient-specific and individualized approaches are also an integral part of the treatment process.

Study Limitations

This expert-based survey provides valuable insights into real-world perioperative strategies in uveitic cataract surgery. Nevertheless, this study has limitations. Firstly, the survey allowed participants to select multiple response options but did not include open-ended questions. While this design facilitates the identification of general trends, it limits the ability to determine the order of preference, frequency of use, or primary strategy employed by each clinician. Furthermore, it potentially restricted the reporting of non-conventional or varied approaches beyond the scope of the predefined answer choices. Secondly, the modest sample size (n=20) may limit the generalizability of the findings. This limitation reflects the inherent challenge of conducting surveys in highly specialized fields such as uveitis, where the pool of qualified respondents is limited. Finally, the institutional context (e.g., university hospitals, public referral centers, private clinics) was not evaluated as a variable in this study. The influence of perioperative decision-making may be attributed to variations in institutional resources, local treatment protocols, and patient demographics. The absence of stratification based on practice setting may have resulted in unmeasured confounders, complicating interpretation of treatment preferences and observed patterns.

Conclusion

This survey highlights prevailing trends and variations in the perioperative management of uveitic cataract surgery, offering a structured overview of current practices among experienced uveitis specialists. A strong consensus was observed in key areas, including the recommended preoperative quiescent period, the continuation of conventional IST, and IOL preferences in JIA-associated uveitis, reflecting shared principles in core decision-making domains. Conversely, notable divergence was identified

in preoperative topical steroid use, NSAID prophylaxis for CME, and strategies for managing postoperative recurrences. These domains, which are characterized by variability and an absence of standardized protocols, may serve as valuable focal points for future prospective studies aiming to establish more definitive guidelines. While personalized care remains paramount, in the absence of universally accepted guidelines, expert consensus continues to serve as a critical reference point, supporting the refinement of perioperative strategies in this complex and nuanced field.

Ethics

Ethics Committee Approval: The ethical approval was not required in this instance, as the expert survey did not involve the use of patient data and guaranteed the anonymity of the participants.

Informed Consent: Not necessary.

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Declarations

Authorship Contributions

Concept: B.Y.O., Design: B.Y.O., Data Collection or Processing: B.Y.O., Analysis or Interpretation: B.Y.O., Ç.A., Literature Search: B.Y.O., Writing: B.Y.O., Ç.A.

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Internal Drainage of Subretinal Fluid Using 25/32 Gauge Cannula in Eyes with Rhegmatogenous Retinal Detachment

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Abstract

Objectives: To evaluate the safety and efficacy of a modified novel surgical approach for the drainage of subretinal fluid (SRF) during pars plana vitrectomy (PPV) for the repair of rhegmatogenous retinal detachment.

Materials and Methods: This retrospective consecutive interventional case series included 15 eyes of 15 consecutive patients who were followed for at least 3 months. All patients underwent 25-gauge (G) PPV with retinal penetration using 25/32G subretinal cannula and SRF aspiration. Laser photocoagulation was not applied around the drainage area in any case. Primary outcomes included visual acuity and the presence of SRF at 1 month.

Results: SRF was not detected in any case at postoperative 1 month. Mean ($\pm$ standard deviation) logarithm of the minimum angle of resolution visual acuity improved from 1.44 ± 1.11 to 0.43 ± 0.59 at the last visit ($p < 0.01$). Cataract surgery was performed in the same sitting in 5 of 11 phakic eyes (45%). Single-site drainage was effective in 11 eyes (73.4%) while two-site drainage was performed in the remaining 4 eyes (26.6%). Retinal pigment epithelium defects were observed at the drainage site in 3 eyes (20%). During follow-up, redetachment due to proliferative vitreoretinopathy occurred in one case (6.6%) and epiretinal membrane in 2 cases (13.3%). Cataract developed in 3 of the 6 remaining phakic eyes (50%).

Conclusion: Transretinal drainage of SRF with the assistance of 25/32G subretinal cannula is effective with low complication rates. This drainage technique may positively affect early postoperative outcomes.

Keywords: Vitrectomy, internal drainage, rhegmatogenous retinal detachment, subretinal cannula, subretinal fluid drainage

Introduction

Drainage of subretinal fluid (SRF) is one of the critical steps in pars plana vitrectomy (PPV) for rhegmatogenous retinal detachment (RRD). Residual SRF may cause retinal displacement and delay visual recovery up to one year.^{1,2} SRF may be drained through existing breaks with or without the help of heavy perfluorocarbon liquid (PFCL) or via a posterior drainage retinotomy under air. Herein, we report our technique for internal SRF drainage using a 25/32-gauge (G) subretinal cannula during vitrectomy.

Materials and Methods

Consecutive patients with RRD were included in the study. Patients with giant retinal tears and pediatric patients were not included. All cases underwent 4-port 25G PPV with chandelier illumination. Phacoemulsification and intraocular lens implantation were performed in the same sitting in eyes with significant cataracts.

The tenets of the Declaration of Helsinki were adhered to throughout data collection and analysis. University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital review board approval (approval number: KAEK/2024.04.86, date: 21.04.2024) and informed consent from each patient were obtained regarding the surgical technique.

Statistical Analysis

Statistical analysis was done with SPSS for Windows 20 (IBM Corp., Armonk, NY). Change in the mean visual acuity was assessed with paired t-test. $P < 0.05$ was considered significant.

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Surgical Technique

A central vitrectomy was performed with a 7,500/min cut rate and 500 mmHg aspiration pressure. PFCL was injected over the posterior pole and SRF aspiration was done through the existing retinal tears using a vitrectomy probe. Peripheral vitrectomy was completed with indentation at a cut rate of 10,000/min. In eyes without detected retinal tear, no effort was made to drain SRF through a tear as the SRF leaked through small peripheral retinal breaks during peripheral vitrectomy with indentation. Fluid-air exchange was started by holding the tip of the backflush cannula at the level of the retinal tear and moving it posteriorly as the fluid level decreased. In eyes with multiple retinal breaks, the most posterior break was selected for SRF drainage. Following aspiration of the preretinal fluid, the PFCL was completely aspirated. A 25G subretinal cannula with a tip size of 32G was inserted and used to penetrate the retina just outside the macula where the SRF level was highest. If resistance was encountered when attempting to penetrate the retina, the cannula tip was slightly beveled using scissors. The SRF was actively aspirated with a vacuum force between 300 mmHg and 500 mmHg. As the SRF was aspirated, the cannula was slowly advanced to keep the tip under the retina when necessary. If there was still a significant amount of SRF at another site after the first aspiration, a second retinal penetration was performed at this site to aspirate the remaining SRF. This ensured near total aspiration of SRF. The steps of SRF drainage with a subretinal cannula are shown in [Figures 1](#) to [3](#).

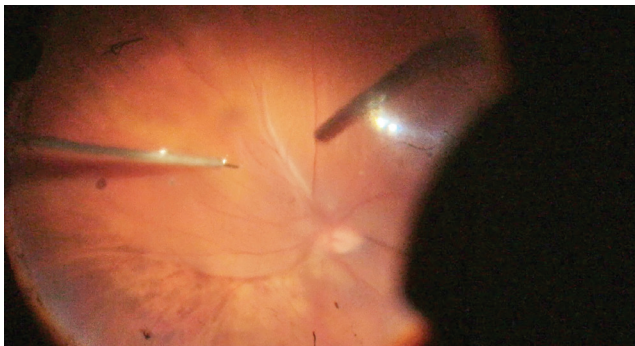


Figure 1. Penetration of the retina with 25/32G cannula after fluid air exchange where subretinal fluid level is high
G: Gauge

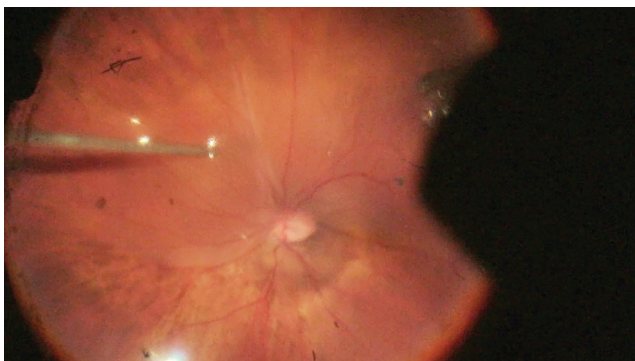


Figure 2. Aspiration of subretinal fluid

Results

We performed this technique in 15 eyes of 15 patients with RRD. Preoperative clinical characteristics are shown in [Table 1](#). The eyes were equally distributed according to laterality. The macula was detached in 10 eyes (66.6%). Four of the macula-on cases had superior, and the other case had superotemporal bullous retinal detachments.

Successful anatomical reattachment and postoperative visual function improvement were achieved in all patients following surgery. Recurrent retinal detachment occurred in one case due to proliferative vitreoretinopathy 3 months after primary surgery. This patient had a 3-month history of total retinal detachment with subretinal membranes before the first surgery. She underwent inferior retinectomy with removal of the subretinal membranes and heavy silicone oil injection as the second surgery. Retinal reattachment was achieved in this case. Slight RPE damage and gliosis occurred at the drainage site in 3 eyes (20%) ([Figure 4](#)).

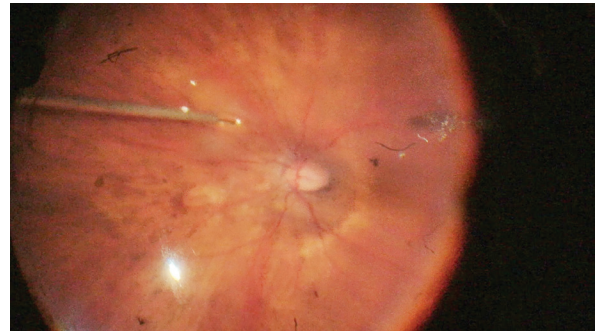


Figure 3. Near complete aspiration of subretinal fluid with the cannula kept steadily in the same position

Table 1. Preoperative patient characteristics	
	Number (%) or mean (range)
Eyes	15
Age (years)	52 (18-76)
Male gender	12 (80)
Pseudophakia	3 (20)
Axial length (mm) (7 patients)	25.12 (21.7-30.6)
Duration of RRD (days)	18.6 (2-90)
Number of tears	
1	5 (33.3)
2	4 (26.6)
≥3	4 (26.6)
Unidentified	2 (13.3)
Number of quadrants involved	
1	2 (13.3)
2	4 (26.6)
3	5 (33.3)
Total	4 (26.6)
Macula-off	10 (66.6)
RRD: Rhegmatogenous retinal detachment	

There was no SRF in any of the eyes at the postoperative 1-month visit. Silicone oil was removed in all cases except the case with recurrent retinal detachment. Results are summarized in [Table 2](#).

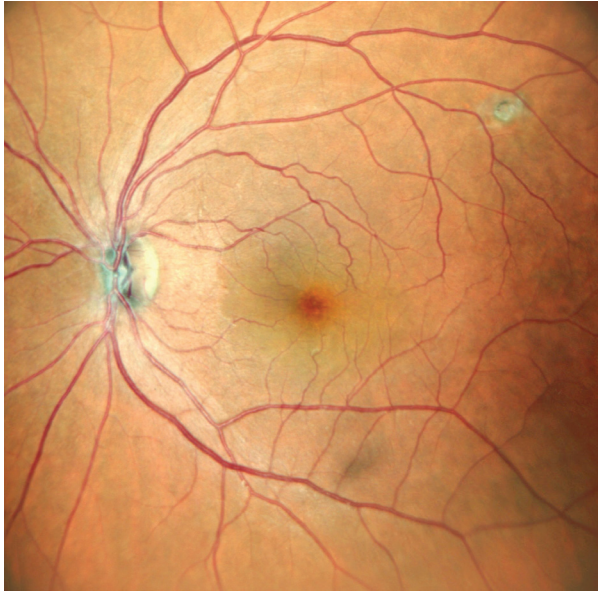


Figure 4. Slight gliosis and retinal pigment epithelium damage at the superotemporal drainage site in a patient with macula-off rhegmatogenous retinal detachment

Table 2. Results	
	Mean $\pm$ SD
logMAR BCVA	1.44 $\pm$ 1.11
Preoperative	0.43 $\pm$ 0.59
Postoperative	p<0.01
Follow-up (months)	8.15 $\pm$ 5.8 (range, 3-20)
	n (%)
Cataract surgery in the same sitting	5/11 phakic eyes (45%)
Tamponade	
Silicone oil	4 (26.6)
Heavy silicone oil	2 (13.3)
C ₃ F ₈	7 (46.6)
SF ₆	2 (13.3)
Number of drainage sites	
1	11 (73.4)
2	4 (26.6)
Complications	
Subretinal hemorrhage	None
RPE defect at drainage site	3 (20.0)
ERM	2 (13.3)
Cataract requiring surgery (n=6)	3 (50)
Recurrent retinal detachment	1 (6.6)

SD: Standard deviation, logMAR: Logarithm of the minimum angle of resolution, BCVA: Best corrected visual acuity, RPE: Retinal pigment epithelium, ERM: Epiretinal membrane

Discussion

Drainage of SRF is a critical step of retinal detachment surgery. Residual SRF may cause retinal folds, retinal displacement, delayed visual recovery, and rarely macular hole formation. These suboptimal surgical outcomes may be detrimental to the visual quality of the patient. Two methods for internal drainage of SRF are utilized in cases with RRD: through an existing retinal break or through a posterior drainage retinotomy. Both have advantages and disadvantages.

Drainage through existing retinal tears may be performed either with active aspiration through the break or by expressing the SRF through the tear with generous use of heavy PFCL. There is almost always some remaining SRF after fluid-air exchange with or without the use of PFCL. SRF drainage using PFCL may also cause retinal displacement, metamorphopsia, and aniseikonia.² Retained PFCL may cause inflammation, and subretinal migration of PFCL may cause significant visual loss.³⁻⁵ Limited use of PFCL decreases the risk of subretinal migration and retention. Subretinal PFCL migration did not occur in any of our cases, including the case with subretinal bands.

On the other hand, posterior drainage of SRF through a larger retinotomy may cause epiretinal membrane (ERM) formation, visual field loss, and enlargement of the laser scars that are applied around it.^{6,7} The 1- and 2-year results of the ELLIPSOID Study compared visual outcomes and outer retinal integrity in eyes with macula-off retinal detachment that underwent SRF drainage either with PFCL, through posterior retinotomy, or through existing tears.^{7,8} It was observed that SRF drainage with PFCL caused the highest rate of interdigitation zone discontinuity and cystoid macular edema, while posterior retinotomy caused significantly higher ERM formation.^{7,8} Kanavati et al.⁹ reported lower retinal displacement but higher retinal fold rates with posterior drainage retinotomy compared to drainage from existing tears. Our technique offers the advantage of enabling near-complete draining of SRF without causing significant retinal damage or membrane formation.

Drainage of SRF with the assistance of 25/32G subretinal cannula technique can be performed effectively as part of PPV in cases with retinal detachment. Desira et al.¹⁰ reported successfully using a 41G cannula for SRF drainage in some of their cases. Bansal et al.¹¹ published the results of SRF drainage with the same approach using a 38G polytip cannula. Consistent with our experience, they reported that extended aspiration time was the drawback of their technique. It is obvious that aspiration time will be longer using a 38G or 41G cannula. The 32G cannula used in our technique allowed us to aspirate the SRF quickly, without losing the continuity of fluid flow.

The risk of retinal displacement is lower in macula-on cases. Shiragami et al.¹² reported downward retinal displacement after PPV for retinal detachment surgery. The risk of retinal displacement was 10.9 times higher in macula-off cases than macula-on cases. Lee et al.¹³ reported significant foveal displacement in 2 of 12 cases (16.6%) without preoperative foveal involvement. These cases had superior or superotemporal

retinal detachments, as in our cases. We preferred to use our drainage technique even in fovea-on cases to reduce the possibility of macular complications.

Our modification of the SRF drainage technique has advantages such as not requiring laser photocoagulation at the site of retinal penetration, limited use of PFCL, and rapid, near-complete aspiration of SRF with minimal exchange of tools.

Potential hazards of this technique are RPE damage and subretinal hemorrhage. These risks can be minimized using a chandelier light and controlled advancement of the cannula. Another disadvantage is the cost of the subretinal cannula.

Study Limitations

This is a non-comparative study which included a limited number of patients. The study also has a short mean follow-up time. We did not evaluate the effect of transretinal SRF drainage on metamorphopsia, which is one of the main postoperative issues in RRD. The effectiveness of this technique could be further evaluated in a larger study with longer follow-up evaluating not only anatomical but also functional outcomes.

Conclusion

Drainage of SRF with a 25G/32G subretinal cannula may be considered as a safe and effective alternative to other internal drainage techniques in eyes with RRD.

Ethics

Ethics Committee Approval: The tenets of the Declaration of Helsinki were adhered to throughout data collection and analysis. University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital review board approval (approval number: KAEK/2024.04.86, date: 21.04.2024).

Informed Consent: Informed consent from each patient were obtained regarding the surgical technique.

Declarations

Authorship Contributions

Surgical and Medical Practices: Z.K., Concept: Z.K., Design: Z.K., Data Collection or Processing: T.A., N.A.G., N.S., Analysis or Interpretation: Z.K., T.A., Literature Search: T.A., Writing: Z.K., T.A., N.A.G., N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Diabetic Retinopathy Screening Approaches in Developing Countries: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Diabetic retinopathy (DR) is one of the primary causes of vision loss among people living with diabetes and is expected to rise globally in the coming years. Effective screening strategies are essential, particularly in developing countries where resources and access to specialized care are limited. Our objective was to assess how accurately different screening methods detect DR, specifically artificial intelligence (AI)-based tools, portable fundus cameras, and trained non-ophthalmologist personnel, implemented in a developing country.

Materials and Methods: A literature search was conducted in ScienceDirect, PubMed, and the Cochrane Library. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. While all included studies were reviewed qualitatively, only those evaluating AI-based screening tools were included in the meta-analysis. Meta-analysis was performed using MetaDisc 2.0 to calculate pooled sensitivity, specificity, diagnostic odds ratio, and likelihood ratios for any DR, referable DR, and vision-threatening DR.

Results: A total of 25 studies were included, with 21 AI-based studies eligible for the meta-analysis. The pooled sensitivity and specificity respectively were 0.890 (95% confidence interval [CI]: 0.845-0.924) and

0.900 (95% CI: 0.832-0.942) for any DR, 0.933 (95% CI: 0.890-0.960) and 0.903 (95% CI: 0.871-0.928) for referable DR, and 0.891 (95% CI: 0.393-0.990) and 0.936 (95% CI: 0.837-0.977) for vision-threatening DR. Meta-regression identified camera type as a significant factor. Portable fundus cameras and general physicians showed good agreement with the gold standards.

Conclusion: These findings support the potential of AI-assisted DR screening in low-resource settings and highlight the complementary roles of portable imaging and task-shifting to trained non-specialists.

Keywords: Diabetic retinopathy screening, artificial intelligence, portable fundus camera, non-specialist, developing countries

Introduction

Diabetes mellitus (DM) is a long-term metabolic disorder that may result in microvascular and macrovascular complications. As living standards have improved significantly, changes in dietary habits and lifestyles have contributed to a steady rise in the prevalence of DM. The primary microvascular complication associated with DM is diabetic retinopathy (DR). It is the leading cause of vision impairment among adults and older individuals.¹ The global incidence of DR is expected to rise significantly, increasing from approximately 103 million people in 2020 to an estimated 130 million by 2030 and nearly 161 million by 2045.^{2,3} Meanwhile, cases of vision-threatening diabetic retinopathy (VTDR) are projected to grow by 26.3%, reaching 36 million by 2030 and 44.82 million by 2045.³

The ideal method for diagnosing DR is a thorough eye examination with pupil dilation, performed by an ophthalmologist utilizing either an indirect ophthalmoscope or a slit lamp biomicroscope. However, various obstacles limit optimal DR screening, such as limited healthcare access, time

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limitations, substantial personnel costs, insufficient awareness and comprehension, and inadequate care coordination.⁴ In clinical trials, the Early Treatment Diabetic Retinopathy Study (ETDRS) seven-standard field protocol, comprising 7 stereoscopic 30-degree fundus photographs, has long been considered the benchmark for DR assessment. Nevertheless, single-field fundus imaging is a practical and effective alternative, particularly considering the logistical, financial, and time-related limitations that make the ETDRS approach unsuitable for routine screening.⁵

The current recommended guidelines for DR management strategies strongly focus on screening and fundus evaluation. Recent technological advancements, including improved camera technology and artificial intelligence (AI), are becoming more affordable and accessible in low- and middle-income countries. Digitizing health records for individuals with DR would support the creation of a registry, allowing for efficient patient tracking, monitoring disease progression, and assessing referral and treatment outcomes.⁶ Therefore, this study aimed to present an overview of the implementation of DR screening modalities in developing countries, including using AI, fundus camera technology, and other community-based screening, and compare them to opportunistic-based screening approaches.

Materials and Methods

Data Sources and Search Strategy

This review followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^{7,8} The study was registered in the International Prospective Register of Systematic Reviews (CRD420251007510). Seven reviewers independently searched for studies published in PubMed, ScienceDirect, and the Cochrane database for relevant articles. The following search terms were used to identify potentially relevant articles: “diabetic retinopathy” AND “screening” AND “community based” OR “telemedicine” OR “teleophthalmology” OR “artificial intelligence” OR “camera” AND “developing countries” OR “low-income countries” OR “middle income countries.” The terms from each category were independently compared and cross-referenced with those from other categories.

Selection Criteria and Selection

This systematic review and meta-analysis included studies conducted in developing countries (i.e., low- and middle-income countries) that involved participants with type 1 or type 2 DM, and provided data on the sensitivity, specificity, or agreement level of the screening methods used. The screening modalities included AI, telemedicine, camera technology, or other community-based programs. The selected studies must have also compared these interventional screening modalities with standard care screening. The “developing countries” in this research were classified based on World Bank data when the studies were conducted. Any country categorized as a low- or middle-income country was included under the term “developing countries.”

Studies were excluded if they lacked sufficient data, focused solely on the prevalence of DR or on comorbid eye diseases, or were case reports, guidelines, editorials, commentaries, opinions, or reviews. Titles and abstracts of the selected articles were screened by seven reviewers, with full texts of potentially eligible studies examined for final inclusion. Any disagreements were resolved through discussion.

Quality Assessment

The seven reviewers independently assessed the quality of all included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.⁹ The QUADAS-2 scale comprised four bias risk assessment domains: patient selection, index test, reference standard, and flow and timing. Each domain included two or three individual questions. Risk in a domain was considered low if all questions were answered affirmatively. This scale also evaluated applicability of the study based on patient selection, index test, and reference standard.

Data Extraction and Analysis

After article selection, the seven reviewers summarized and extracted data related to the screening methods’ diagnostic accuracy. These data included total participants, the country where the study was conducted, interventional screening methods, technical characteristics (pupil dilation status, AI system, device), indicators measured, and outcomes such as DR type, sensitivity, specificity, and agreement. Since not all studies analyzed each of these indicators, our meta-analysis was further divided into subgroups based on the available uniform indicators. We used the web application MetaDisc 2.0 for the outcome variables of true positives, false positives, false negatives, and true negatives. We also generated a summary receiver operating characteristic (SROC) curve and forest plots to visualize the pooled results. The bivariate I^2 test was used to assess heterogeneity resulting from a potential non-threshold effect in this meta-analysis. If I^2 exceeds 50%, it is deemed considerable heterogeneity. MetaDisc 2.0 supports bivariate meta-analysis and provides global heterogeneity (bivariate I^2), but does not compute subgroup-specific I^2 directly.

Next, subgroup analysis and meta-regression techniques (pupil dilation status, AI algorithm, and camera device) were applied to diagnostic accuracy and heterogeneity to evaluate the possible impact of the covariates. This approach allowed us to maximize its diagnostic meta-analysis strength while acknowledging its limitations. To assess diagnostic accuracy, a bivariate random-effects model was employed to derive pooled sensitivity, specificity, diagnostic odds ratio (DOR), and likelihood ratios (LR+ and LR-). The area under the SROC curve reflected the AI’s performance in diagnosing DR.

Results

Study Selection and Characteristics

[Figure 1](#) summarizes the literature search and selection process. Initially, a total of 3,216 relevant articles were identified from the specified databases using a structured retrieval approach.

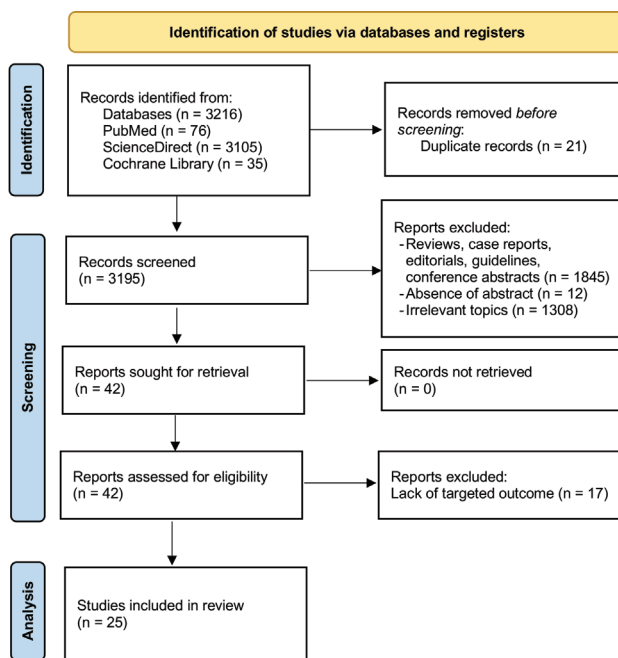


Figure 1. The study identification and selection process

Studies that were duplicates, conference abstracts, or one of the article types specified in the exclusion criteria (case report, guideline, editorial, commentary, opinion, or review, including meta-analysis), those without available full texts, and those with titles or abstracts unrelated to our review were excluded. After this initial screening, 42 original studies remained. Further evaluation led to the exclusion of papers with unclear methodologies or incomplete or irrelevant targeted outcomes.

The characteristics of the remaining 25 studies are summarized in [Table 1](#). These studies used several screening modalities for detecting DR: 21 evaluated the accuracy of AI-based/assisted screening, 2 assessed the accuracy of handheld/smartphone-based fundus cameras, and 2 reported about empowering trained general physicians to enhance the coverage of DR detection. The studies were performed in developing countries in Asia (China, India, Sri Lanka, Philippines, and Thailand), South America (Brazil and Mexico), and Africa (Zambia and Kenya). The primary goal of screening studies involving general physicians using an AI-based portable device was to evaluate and compare their accuracy to standard care for identifying any grade of DR, referable diabetic retinopathy (RDR), and VTDR. Most studies employed the International Clinical Diabetic Retinopathy Severity Scale classification system, where moderate nonproliferative diabetic retinopathy (NPDR) or worse was considered RDR, and severe NPDR or worse was considered VTDR. We included more-than-mild DR in the RDR group.

Quality Assessment

Twenty-five studies were reviewed for methodological quality and potential bias, following the QUADAS-2 guidelines. The evaluation revealed a risk of patient selection bias in

approximately 40% of the studies ([Figure 2](#)). An overview of the quality assessment for each study is provided in [Figure 3](#). For the remaining three domains (index test, reference standard, and flow and timing), the results suggested a generally low risk of bias and few issues with applicability. No studies were excluded following the quality assessment.

The Performance of Screening Modalities for Detecting Diabetic Retinopathy

Twenty-one studies were included in the final meta-analysis stage. These studies evaluated the performance of AI-based/assisted screening for DR in developing countries compared to standard/reference screening methods. They reported the performance of AI in detecting RDR (n=18), VTDR (n=3), and DR of any severity (n=11). We further evaluated AI's performance in detecting any DR and RDR based on pupil dilation status (mydriatic or non-mydriatic), algorithm (convolutional neural network [CNN] or deep learning [DL]), and camera device (smartphone-based/portable retinal camera or retinal fundus camera). Studies where pupil dilation was performed only when necessary were classified under the non-mydriatic group, whereas those employing combined methods were included in the mydriatic group. Most studies excluded ungradable images, while some performed analyses with and without the ungradable images. In this review, we only included the results for gradable images (see [Table 2](#)).

We used MetaDisc 2.0 to analyze the performance of AI-based screening in the included studies. [Table 2](#) presents the pooled sensitivity, specificity, DOR, LR+, LR-, and I^2 for any DR, RDR, and VTDR. The forest plots of sensitivity, specificity, and SROC curve are shown in [Figures 4, 5, and 6](#), respectively. The SROC curves illustrate the overall diagnostic performance of AI models for detecting any DR and RDR. The SROC curve for RDR demonstrates a more concentrated confidence ellipse, indicating greater consistency across studies. In contrast, the wider prediction ellipse in the any-DR SROC suggests higher variability in diagnostic accuracy. This variability may reflect differences in study populations, image quality, or AI model architectures. Overall, the AI models exhibited more stable and reliable performance in detecting RDR, whereas their effectiveness in identifying any DR appears more heterogeneous.

The I^2 values were high overall, with 0.809 for any DR and 0.82 for RDR, indicating substantial heterogeneity. We also performed a meta-regression with MetaDisc 2.0 using the subgroup analysis parameters to explore potential sources of heterogeneity. The outcomes are presented in [Tables 3 and 4](#). For the meta-regression analysis, only studies utilizing CNN or DL algorithms were included for the AI algorithm covariate because one study employed a machine learning approach, which was insufficient to form a meaningful subgroup or allow for reliable meta-regression. In addition, one study was also excluded from the meta-regression evaluating pupil dilation status and camera type because it did not clearly state whether images were obtained using a mydriatic or non-mydriatic method, nor did it specify the type of camera used.

Table 1. Characteristics of the studies assessing the performance of diabetic retinopathy screening methods

Author, year	Country	Study design	Image acquisition	Intervention screening	Reference screening	Device/AI used	Evaluated metric	Participants	Classification
Bellemo et al. ³⁸ , 2019	Zambia	Cross-sectional	The digital retinopathy system fundus camera; NM	Mobile screening, AI-algorithm (CNNs)	Retinal specialist	Adapted VGGNet architecture + ResNet architecture	Sensitivity, specificity, AUC, heatmaps for detecting RDR, and VTDR	1,574	ICDRSS
Natarajan et al. ³⁶ , 2019	India	Prospective cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); NM	AI-algorithm (CNNs)	Vitreoretinal resident and surgeon	Medios AI (Remidio)	Sensitivity, specificity, for detecting DR and RDR	231	ICDRSS
Nunez do Rio et al. ³⁷ , 2022	India	Prospective cross-sectional	Retinal fundus camera (Topcon NW400); NM	AI-algorithm (DL)	Trained optometrist or ophthalmologist	VISUHEALTH-AI DR (software version 1.8)	Sensitivity, specificity for detecting RDR	11,199	ICDRSS
Gulshan et al. ³⁸ , 2019	India	Prospective observational	Retinal fundus camera (NMTRC; Topcon Medical Systems; 3nethra; Forus Health); NM	AI-algorithm (DL)	Trained grader and retinal specialist	NA	Sensitivity, specificity for detecting RDR	3,049	ICDRSS
Ruamviboonsuk et al. ³⁹ , 2022	Thailand	Prospective interventional cohort	Retinal fundus camera (Topcon Maestro 3D OCT-1, Topcon TRC-NW300, Nidek AFC-230, Nidek AFC-210, and Nidek AFC-300), MD when needed	AI-algorithm (DL)	Retinal specialist	NA	Sensitivity, specificity, PPV, NPV for detecting RDR	7,651	ICDRSS
Sosale et al. ⁴⁰ , 2020	India	Cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); NM	AI-algorithm (CNNs)	Retinal specialist	Medios AI	Sensitivity, specificity, PPV, NPV for detecting any DR, RDR, and VTDR	900	ICDRSS
Penha et al. ²² , 2023	Brazil	Retrospective	Smartphone-based fundus camera (Eyer, Phelcom); MD	AI-algorithm (CNNs)	Retinal specialist	EyerMaps, Phelcom Technologies	Sensitivity, specificity, PPNV, NPV for detecting mtmDR	686	ICDRSS
Jain et al. ²¹ , 2021	India	Cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); MD	AI-algorithm (CNNs)	Retinal specialist	Medios AI (Remidio)	Sensitivity, specificity, heatmaps for detecting RDR	1,294	ICDRSS
Pawar et al. ²³ , 2021	India	Cross-sectional	Portable fundus camera (Intucam Prime); Combined (MD > NM)	AI-algorithm (DL)	Ophthalmologist	NA	Sensitivity, specificity for detecting RDR	138	ICDRSS
Noriega et al. ²⁹ , 2021	Mexico	Randomized controlled	NA	AI-algorithm (DL)	Ophthalmologist and retina specialists	ARIA system	Sensitivity, specificity, and heatmaps for detecting RDR	100	ICDRSS

Table 1. Continued

Author, year	Country	Study design	Image acquisition	Intervention screening	Reference screening	Device/AI used	Evaluated metric	Participants	Classification
Pei et al. ⁴¹ , 2022	China	Cross-sectional	Retinal fundus camera (Zeiss Non-mydiatic Fundus Camera); NM	AI algorithm (DL)	Ophthalmologist	EyeWisdom DSS and EyeWisdom MCS	Sensitivity, specificity, AUC, PPV, NPV, kappa test for detecting Any DR, NPDR, PDR	549	ICDRSS
Dong et al. ⁴² , 2022	China	Cross-sectional	Retinal fundus camera (RetiCam 3100); NM	AI algorithm (CNN)	Ophthalmologist and retinal specialist	CARE system	Sensitivity, specificity, PPV, NPV for detecting any DR, mmdr, VTDR, DME	443	ICDRSS
Ming et al. ⁴³ , 2021	China	Prospective cross-sectional	Retinal fundus camera (Canon CR-2 Digital Retinal Camera); NM	AI algorithm (DL)	Ophthalmologist	EyeWisdom	Sensitivity, specificity, AUC for detecting any DR and RDR	173	ICDRSS
Zhang et al. ⁴⁴ , 2020	China	Prospective cross-sectional	Retinal fundus camera (Topcon TRC-NW400, MiiS DSC-200, Canon CR-2 PLUS AF, Canon CR-2 AF and Zeiss VISUCAM200); NM	AI algorithm (DL)	Ophthalmologist	VoxelCloud Retina	Sensitivity, specificity, PPV, NPV for detecting RDR	40,665	ICDRSS
Li et al. ⁴⁵ , 2021	China	Prospective cross-sectional	Retinal fundus camera (KOWA nonmyd WX); NM	AI algorithm (DL)	Retinal specialist	VoxelCloud Retina	Sensitivity, specificity, AUC for detecting RDR	1,147	ICDRSS
Bawankar et al. ⁴⁶ , 2017	India	Prospective open-label	Portable fundus camera (Bosch non-mydiatic fundus camera); NM and 7-Standard Field stereoscopic Digital Color Fundus (reference); MD	AI algorithm (CNNs)	Ophthalmologist	Bosch DR Algorithm	Sensitivity, specificity, PPV, NPV for detecting any DR	560	ETDRS
Yang et al. ²⁴ , 2022	China	Prospective observational controlled	Retinal fundus camera (Zeiss VisuCam FF450, Topcon TRC-50DX, Topcon NW-400); MD	AI algorithm (CNNs)	Ophthalmologist	AIDRScreening system v. 1.0	Sensitivity, specificity, PPV, NPV for detecting RDR	962	COS guidelines
Al Turk et al. ⁴⁷ , 2020	China, Kenya	Retrospective	Retinal fundus camera (Optovue iCam, Centervue DRS, Topcon NW and Canon CR1/DGi/CR2); NM	AI algorithm (CNNs)	Ophthalmologist	DAPHNE	Sensitivity, specificity, kappa agreement test for detecting RDR, PDR	39,700	NSC (China), ICDRSS (Kenya)

Table 1. Continued

Author, year	Country	Study design	Image acquisition	Intervention screening	Reference screening	Device/AI used	Evaluated metric	Participants	Classification
Rajalakshmi et al. ⁴⁸ , 2018	India	Cross-sectional	Smartphone-based fundus camera (Remidio Fundus on Phone); MD	AI algorithm (DL)	Ophthalmologist	EyeArt	Sensitivity, specificity, PPV, NPV, kappa test for detecting any DR, DME, PDR, STDR, RDR	296	ICDRSS
Hansen et al. ⁴⁹ , 2015	Kenya	Retrospective cross-sectional	Retinal fundus camera (Topcon1 NW/6S non-mydiatic retinal camera); MD	AI algorithm (ML)	Ophthalmologist	Iowa Diabetic Retinopathy (IDP)	Sensitivity, specificity, PPV, NPV for detecting any DR	3,126	ICDRSS
Malerbi et al. ⁵⁰ , 2024	Brazil	Cross-sectional	Smartphone-based fundus camera (The Eyer); MD	AI algorithm (CNN)	Ophthalmologist, retinal specialist	Retinal Alteration Score (RAS), Diabetic Retinopathy Alteration Score (DRAS)	Sensitivity, specificity for detecting any DR and mtrmDR	327	ICDRSS
Salongcay et al. ¹¹ , 2022	Philippines	Prospective cross-sectional	Fundus photography with different handheld retinal cameras; Combined NM and MD	NM and MD handheld retinal imaging	ETDRS 7-field fundus camera	iNview, RetinaVue 700, Smartscope (SSNM), Aurora (AUNM)	Sensitivity and Specificity for detecting any DR, RDR, and VTDR	116	ICDRSS
Wintergerst et al. ¹⁰ , 2020	India	Cross-sectional	All participants were divided into groups with different retinal camera; MD	Four SBFi approaches	Conventional 7-field color fundus photography	Direct SBFi: Peek Retina, D-EYE, a do-it-yourself by Sankara Eye Foundation Indirect SBFi: Paxos Scope	Image quality, examination time, and agreement for detecting any DR, severe DR, DME.	193	ICDRSS
Cunha et al. ¹² , 2018	Brazil	Cross-sectional	Retinal fundus camera (Canon CR-2); NM	Grading by non-ophthalmologist (family physicians)	Grading by ophthalmologist (ophthalmologist and retinal specialist)	NA	Sensitivity, specificity, PPV, NPV, kappa agreement for detecting any DR, DME, NPDR/PDR	200	ICDRSS
Piyasena et al. ¹³ , 2019	Sri Lanka	Cross-sectional	Hand-held non-mydiatic (Visucout 100®-Germany) digital retinal camera; NM	Grading by general physicians	Dilated fundus examination by retinologist using slit-lamp bio-microscopy with a 90D lens and indirect ophthalmoscopy using a 20D lens.	Visucout 100®-Germany	Sensitivity, specificity, PPV, NPV, kappa agreement for detecting any DR, RDR, and maculopathy	700	United Kingdom National Screening System
AI: Artificial intelligence, AUC: Area under the curve, CNN: Convolutional neural networks, COS: Chinese Ophthalmic Society, D: Dioptr, DL: Deep learning, DME: Diabetic macular edema, DR: Diabetic retinopathy, ICDRSS: International Clinical Diabetic Retinopathy Severity Scale, MD: Mydiatic, ML: Machine learning, mtrmDR: More-than-mild diabetic retinopathy, NA: Not available, NM: Non-mydiatic, NPDR: Non-proliferative diabetic retinopathy, NPV: Negative predictive value, NSC: National Screening Committee, RDR: Referable diabetic retinopathy, PDR: Proliferative diabetic retinopathy, PPV: Positive predictive value, SBFi: Smartphone-based fundus imaging, VTDR: vision threatening diabetic retinopathy									

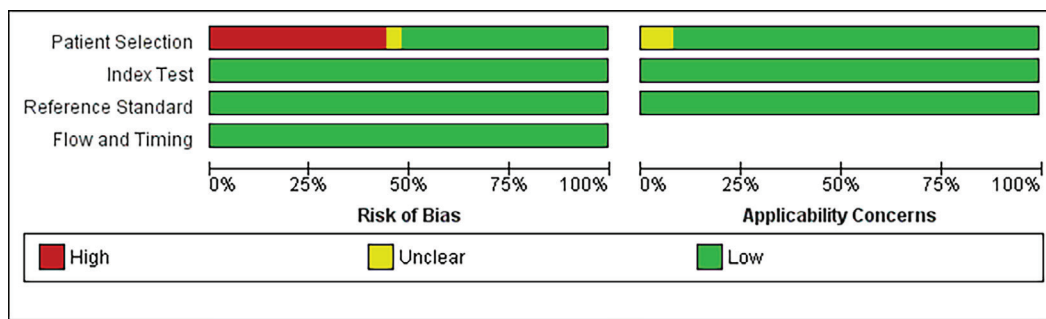


Figure 2. Risk of bias graph chart with QUADAS-2
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2



Figure 3. Risk of bias for individual studies included in the review

These exclusions were made to maintain consistency in covariate classification and preserve the validity of the meta-regression analysis. However, all excluded studies were still included in the overall pooled analysis of diagnostic accuracy. We found that for any DR, none of the covariates significantly explained the heterogeneity. In contrast, for RDR detection, p values indicated statistical significance for camera device ($p < 0.05$), suggesting that variations in the type of camera used for RDR detection could contribute to the heterogeneity across studies.

Two studies evaluated handheld or smartphone-based fundus imaging (SBFI) as a portable device alternative to standard fundus photography. Wintergerst et al.¹⁰ compared four SBFI modalities, three using direct and one using indirect ophthalmoscopy. The images were compared against reference standards of 7-field color fundus photography. Meanwhile, indirect ophthalmoscopy conducted by a specialist was evaluated for image clarity, coverage area, duration of examination, and accuracy in diagnosing DR.

Among 381 eyes of 193 subjects, all SBFI methods produced clear images, but direct SBFI had more artifacts and lower contrast than indirect SBFI. Across different smartphone-based imaging systems, sensitivity for any DR detection ranged from 67% to 79% while specificity remained high, between 98% and 100%. For RDR (moderate NPDR or worse), sensitivity varied between 76% and 87%, with specificity between 96% and 100%. Detection of severe DR (severe NPDR or PDR) achieved 100% sensitivity and specificity with some devices. For diabetic maculopathy, sensitivity ranged from 79% to 83%, while specificity was consistently 100%. The authors concluded that indirect ophthalmoscopy-based SBFI provided the highest diagnostic accuracy, with a strong agreement with the reference standard (Cohen's kappa: 0.868).¹⁰

Salongcay et al.¹¹ evaluated non-mydratic and mydratic handheld retinal imaging versus ETDRS 7-standard field fundus photography in 225 eyes of 116 patients. For detection of any DR, non-mydratic devices demonstrated sensitivities ranging from 80% to 89% and specificities between 88% and 97%. Sensitivity for RDR was 87%-93%, while specificity varied from 76% to 92%. For VTDR (severe NPDR or worse, including PDR and DME), sensitivity ranged from 83% to 88% but specificity was lower, ranging from 69% to 86%. Smartscope NM and Aurora/RetinaVue-700 MD images achieved 80%

Table 2. Results of subgroup analysis for performance of AI-based screening							
Categories	Number of studies	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	DOR (95% CI)	LR+ (95% CI)	LR- (95% CI)	I²
Categories of DR							
Any DR	11	0.890 (0.845-0.924)	0.900 (0.832-0.942)	72.680 (40.102-131.723)	8.867 (5.256-14.956)	0.122 (0.087-0.172)	0.809
RDR	18	0.933 (0.89-0.96)	0.903 (0.871-0.928)	130.617 (74.629-228.609)	9.665 (7.271-12.849)	0.074 (0.045-0.123)	0.82
VTDR	3	0.891 (0.393-0.990)	0.936 (0.837-0.977)	120.198 (7.706-1874.779)	13.972 (5.027-38.834)	0.116 (0.012-1.117)	NA
Pupil dilation status							
Mydriatic							
Any DR	5	0.904 (0.839-0.944)	0.874 (0.747-0.942)	64.965 (27.304-154.574)	7.153 (3.453-14.817)	0.11 (0.066-0.184)	NA
RDR	6	0.963 (0.907-0.986)	0.863 (0.79-0.914)	163.695 (57.747-464.023)	7.047 (4.521-10.985)	0.043 (0.017-0.109)	NA
Non-mydriatic							
Any DR	6	0.877 (0.808-0.924)	0.918 (0.835-0.961)	79.761 (36.096-176.244)	10.663 (5.267-21.587)	0.134 (0.086-0.209)	NA
RDR	11	0.908 (0.84-0.949)	0.92 (0.887-0.944)	113.552 (57.141-225.654)	11.382 (8.048-16.097)	0.1 (0.057-0.177)	NA
AI Algorithm							
Convolutional neural networks							
Any DR	6	0.879 (0.81-0.925)	0.923 (0.851-0.961)	86.348 (50.429-147.851)	11.349 (5.997-21.478)	0.131 (0.086-0.202)	NA
RDR	9	0.934 (0.869-0.968)	0.898 (0.849-0.932)	124.164 (57.798-266.734)	9.158 (6.19-13.549)	0.074 (0.037-0.147)	NA
Deep learning							
Any DR	4	0.929 (0.862-0.964)	0.892 (0.767-0.954)	107.024 (50.597-226.378)	8.572 (3.909-18.799)	0.08 (0.043-0.15)	NA
RDR	9	0.933 (0.864-0.968)	0.909 (0.862-0.941)	138.245 (62.156-307.479)	10.248 (6.78-15.489)	0.074 (0.036-0.152)	NA
Camera device							
Smartphone-based/portable camera							
Any DR	7	0.916 (0.872-0.946)	0.906 (0.822-0.953)	104.602 (57.669-189.729)	9.733 (5.119-18.509)	0.093 (0.063-0.138)	NA
RDR	6	0.97 (0.929-0.988)	0.856 (0.792-0.903)	194.987 (69.095-550.256)	6.75 (4.602-9.901)	0.035 (0.014-0.085)	NA
Retinal fundus camera							
Any DR	4	0.831 (0.735-0.898)	0.885 (0.744-0.953)	37.875 (17.862-80.309)	7.221 (3.234-16.123)	0.191 (0.126-0.289)	NA
RDR	11	0.894 (0.823-0.938)	0.927 (0.897-0.948)	106.674 (52.418-217.09)	12.239 (8.598-17.421)	0.115 (0.068-0.195)	NA
AI: Artificial intelligence, DOR: Diagnostic odds ratio, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, DR: Diabetic retinopathy, RDR: Referable diabetic retinopathy, VTDR: Vision threatening diabetic retinopathy, NA: Not available							

sensitivity and 95% specificity for detecting DR, meeting thresholds for RDR and DME. However, no device met the 95% specificity requirement for VTDR. Non-mydriatic imaging also had higher ungradable rates (15.1%-38.3% for DR) than mydriatic imaging (0%-33.8%).¹¹

Next, two studies evaluated the agreement and diagnostic accuracy of non-ophthalmologists in DR screening. Cunha et al.¹² assessed the efficacy of non-mydriatic fundus photography in DR screening by analyzing the diagnostic agreement across qualified family physicians (FP), general ophthalmologists (GO), and a retinal specialist. A total of 397 eyes of 200 individuals with diabetes were examined. The retinal specialist diagnosed DR in 41.8% of eyes, whereas GO1 and GO2 diagnosed DR in 28.7% and 45.8% of cases, respectively. Diagnostic agreement between the FPs and the retinal specialist for DR diagnosis varied from modest to considerable, with kappa values as follows: FP1 = 0.56, FP2 = 0.69, FP3 = 0.73, FP4 = 0.71. Similarly, agreement in DR severity grading was moderate to substantial

(FP1 = 0.51, FP2 = 0.66, FP3 = 0.69, FP4 = 0.64). However, the agreement for DME diagnosis was lower, varying from fair (FP1 = 0.33, FP2 = 0.39, FP3 = 0.37) to moderate (FP4 = 0.51).¹²

Furthermore, Piyasena et al.¹³ evaluated the diagnostic accuracy of a handheld non-mydriatic fundus camera in Sri Lanka, where nine general physicians were trained by ophthalmologists to perform DR screening. Two physicians with the highest agreement with the retinal specialist ($k = 0.8-0.9$) were selected as final graders. For any DR, sensitivity in non-mydriatic imaging ranged from 78.3% to 82.7%, while specificity ranged from 70.4% to 76.2%. With pupil dilation, sensitivity ranged from 78.0% to 79.3%, and specificity improved to 89.2%-91.5%. The kappa agreement value with a retinal specialist for any DR improved from 0.42-0.47 in non-mydriatic imaging to 0.66-0.68 after pupil dilation. For RDR, sensitivity in non-mydriatic imaging ranged from 84.9% to 86.8%, while specificity ranged from 71.7% to 77.3%. With pupil dilation, sensitivity

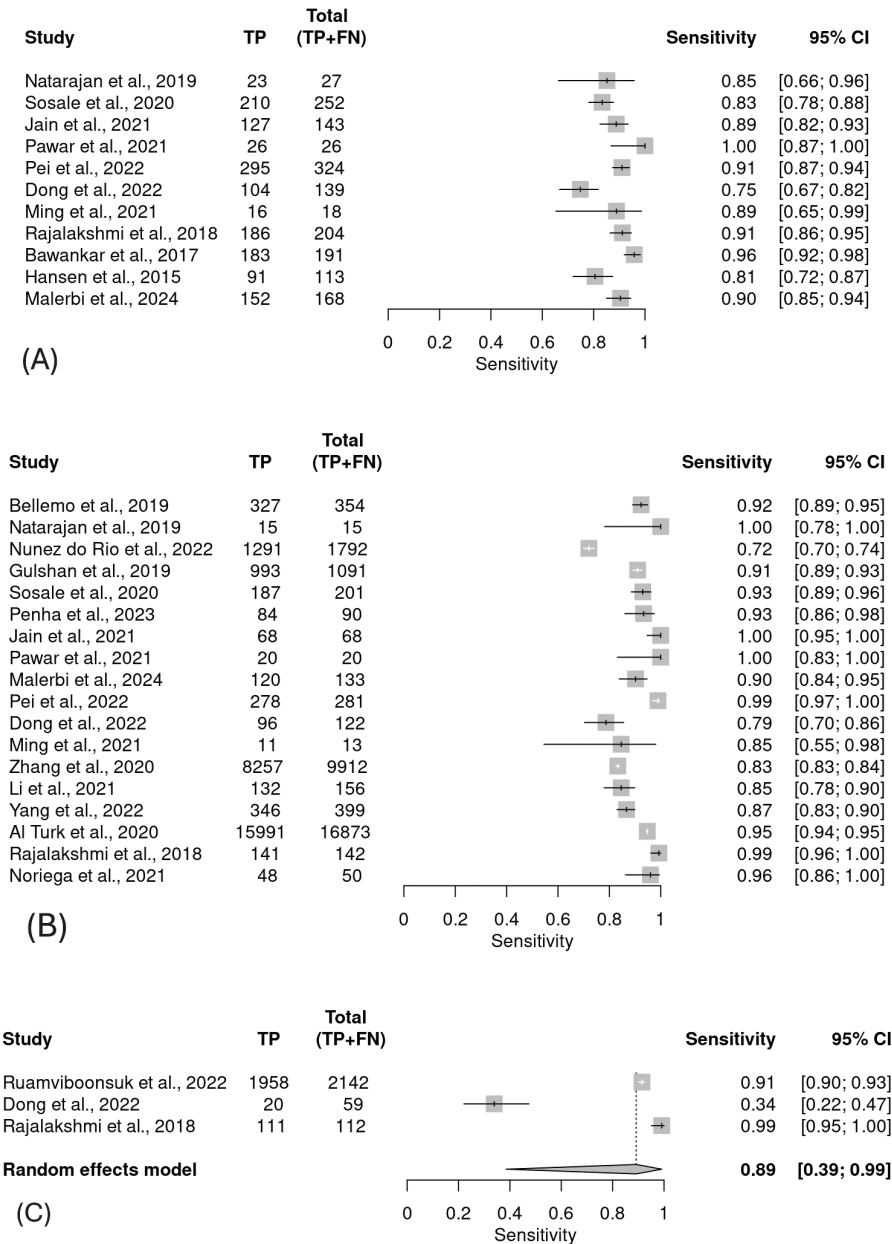


Figure 4. Forest plots of pooled sensitivity in all the studies included in the meta-analysis. A) Forest plot of any diabetic retinopathy (DR). B) Forest plot of referable DR. C) Forest plot of vision-threatening DR
 TP: True positives, FN: False negatives, CI: Confidence interval

improved to 88.7%-92.5% and specificity increased to 94.9%-96.4%. The kappa agreement values for RDR detection were 0.23-0.29 in non-mydratic imaging and increased to 0.68-0.76 in mydratic imaging. For maculopathy detection, sensitivity in non-mydratic imaging was 89.2%, specificity was 70.1%, and the kappa agreement with the reference standard was 0.29. The percentage of ungradable images was 43.4% in non-mydratic imaging and decreased to 12.8% after pupil dilation.¹³

Discussion

This study assessed the diagnostic effectiveness of different DR detection methods to increase screening availability in developing countries. Recent technological advancements hold significant potential to enhance healthcare services, especially in developing countries. This research analyzed 25 studies, of which 21 were included in the meta-analysis and 4 were included in the qualitative review.

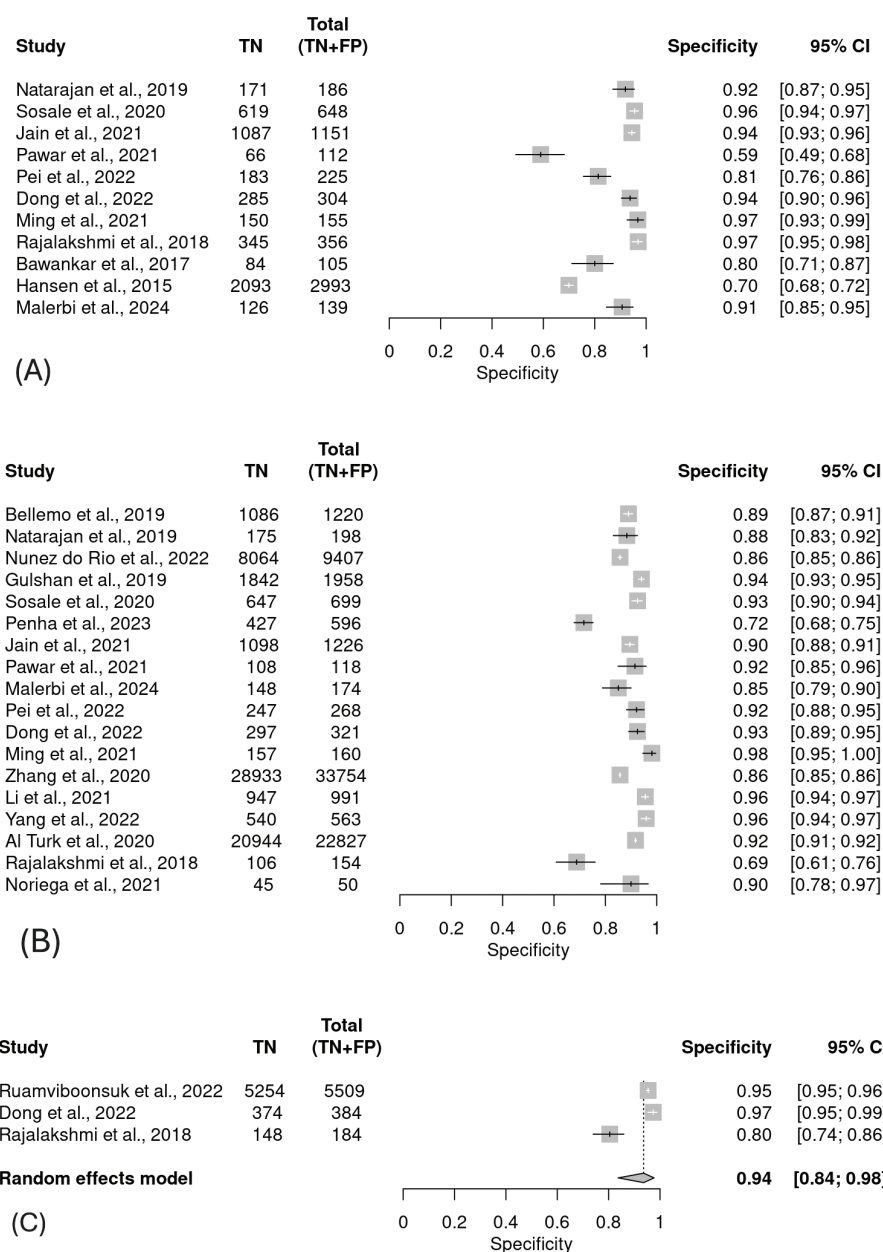


Figure 5. Forest plots of pooled specificity in all the studies included in the meta-analysis. A) Forest plot of any diabetic retinopathy (DR). B) Forest plot of referable DR. C) Forest plot of vision-threatening DR
 TN: True negatives, FP: False positives, CI: Confidence interval

Among the 21 meta-analyzed studies, the diagnostic performance of AI-based/assisted screening demonstrated strong diagnostic ability with a pooled sensitivity of 0.890, specificity of 0.900, and DOR of 72.680 for detecting DR. Similarly, the diagnostic performance of AI-based/assisted screening for detecting RDR had a pooled sensitivity of 0.933, specificity of 0.903, and an even higher DOR of 130.617, demonstrating high accuracy for identifying more severe cases requiring referral.

Meanwhile, although only three studies evaluated VTDR, the pooled results still suggest encouraging performance, with pooled sensitivity at 0.891 and specificity at 0.936, though the limited data warrant careful interpretation. These results exceeded the Food and Drug Administration established 85% sensitivity and 82.5% specificity endpoints.¹⁴ They are also consistent with those found in earlier systematic reviews and meta-analyses that evaluated the diagnostic accuracy of AI algorithms in DR

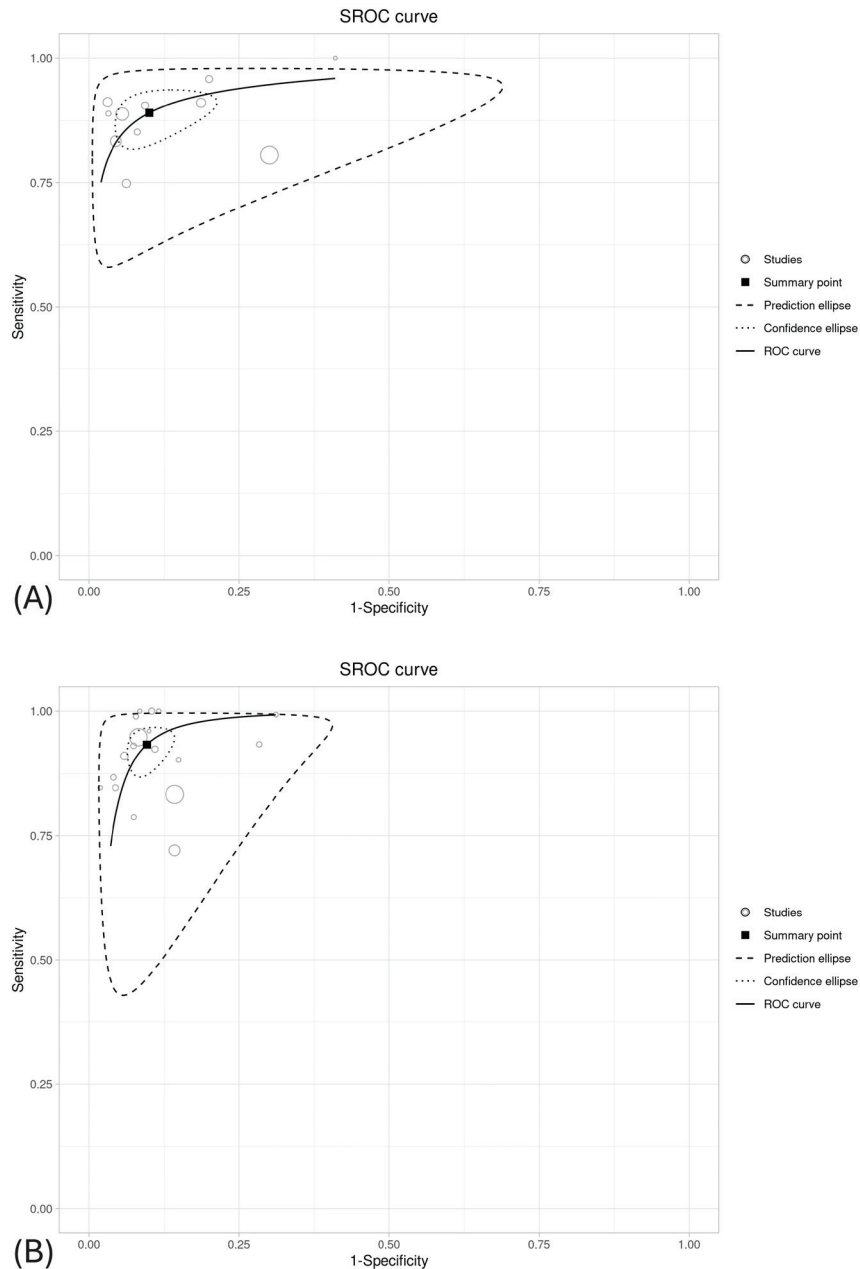


Figure 6. Summary receiver operating characteristic (SROC) curve of included studies in data analysis. A) SROC curve of any diabetic retinopathy (DR). B) SROC curve of referable DR

screening.^{15,16,17} Our results are also comparable to those of meta-analyses on AI-based detection for other eye disease such as glaucoma, pathologic myopia, and dry eye disease.^{18,19,20}

Furthermore, we conducted a subgroup analysis to investigate the factors influencing AI performance in detecting any DR and RDR. AI exhibited similar accuracy in detecting DR from both non-mydratic and mydratic images. Mydratic photographs have slightly better sensitivity but slightly lower specificity than non-mydratic photographs. This result may be because mydriasis produces more detailed images. False positives occur due to subtle lesions or certain non-DR retinal abnormalities

including drusen, atrophy or hypertrophy of the retinal pigment epithelium, telangiectatic vessels near the macula, tessellated fundus, and retinal vein occlusion.^{21,22,23} However, retinal lesions unrelated to DR still indicate that the patient must consult an ophthalmologist or retina specialist. Therefore, they cannot be considered false positives and of no concern in terms of clinical implications. Meanwhile, in non-mydratic photographs, the retinal images tend to be darker, may not capture all subtle DR lesions, and could result in a higher percentage of ungradable images.²⁴

Table 3. Meta-regression of included studies for detecting any diabetic retinopathy

Subgroup	Parameter	Estimate	LCL	UCL	p value
Pupil dilation status^a	Relative sensitivity	1.03	0.945	1.123	0.497
	Relative specificity	0.952	0.84	1.079	0.427
	Global test comparison				0.661
Algorithm^b	Relative sensitivity	0.946	0.872	1.027	0.209
	Relative specificity	1.035	0.923	1.16	0.545
	Global test comparison				0.433
Device^c	Relative sensitivity	1.102	0.991	1.224	0.047
	Relative specificity	1.024	0.898	1.168	0.719
	Global test comparison				0.051

^aWhether pupil dilation is done: non-mydratric or mydratric
^bAlgorithm of the artificial intelligence model used: deep learning and convolutional neural networks
^cDevice used to take retinal photographs: smartphone-based or portable camera and retinal fundus camera
LCL: Lower confidence limit, UCL: Upper confidence limit

Table 4. Meta-regression of included studies for detecting referable diabetic retinopathy

Subgroup	Parameter	Estimate	LCL	UCL	p value
Pupil dilation status^a	Relative sensitivity	1.061	0.992	1.135	0.097
	Relative specificity	0.938	0.869	1.013	0.079
	Global test comparison				0.09
Algorithm^b	Relative sensitivity	1.001	0.932	1.075	0.975
	Relative specificity	0.988	0.928	1.051	0.703
	Global test comparison				0.927
Device^c	Relative sensitivity	1.086	1.015	1.162	0.013
	Relative specificity	0.924	0.862	0.99	0.018
	Global test comparison				0.005

^aWhether pupil dilation is done: non-mydratric or mydratric
^bAlgorithm of the artificial intelligence model used: deep learning and convolutional neural networks
^cDevice used to take retinal photographs: smartphone-based or portable camera and retinal fundus camera
LCL: Lower confidence limit, UCL: Upper confidence limit

For the AI algorithm architecture, there was minimal difference in pooled performance between CNN-based models and broader DL algorithms. The pooled sensitivity for DL models was slightly higher than for CNN models, but CNN models achieved better specificity. However, these differences were not statistically significant. Our results suggested that choosing between DL and a CNN architecture did not contribute substantially to diagnostic performance. DL is an advanced branch of machine learning that utilizes multi-layered neural networks to analyze extensive datasets, allowing systems to identify complex visual patterns autonomously. CNN, a specific DL variant, is optimized for image analysis, especially in medical diagnostics.²⁵ CNN-based models utilize convolutional layers to accurately recognize and categorize retinal abnormalities, including microaneurysms, hemorrhages, and exudates, essential for DR detection.²⁶ Since DL-based models demonstrate greater sensitivity, they may be more appropriate for initial screening to minimize missed cases. On the other hand, CNN models could be utilized as reliable confirmation tools, helping to reduce unnecessary referrals due to false positives. Joseph et al.²⁷ also

reported in their meta-analysis that the DL algorithm, which included CNN, demonstrated high accuracy compared to machine learning. Only one study in our review used machine learning. When this study was excluded, the pooled sensitivity and specificity increased to 90% and 91%, respectively, for detecting any DR. The improved efficiency and diagnostic accuracy of DL over traditional machine learning has revolutionized the ability to detect DR using fundus images.^{25,26,27}

Three studies incorporated AI-generated heatmaps to enhance interpretability in DR screening. Bellemo et al.²⁸ used heatmaps to highlight specific areas in the retinal fundus images that most significantly influence CNN determination. These visualizations illustrate the AI system's decision-making process and explain features that may encourage trust in AI models.²⁸ The heatmaps of the lesions provided by the AI can also be utilized for patient education.²¹ Noriega et al.²⁹ also showed that incorporating attention heatmaps highlighted DR lesions and improved grader sensitivity when used in an assistive screening approach. Sayres et al.³⁰ further investigated the heatmaps' impact on ophthalmologists' grading accuracy and confidence.

They found that while heatmaps improved sensitivity for RDR, they also led to overdiagnosis in cases with no DR, increasing false positives for mild NPDR. This result might be because heatmaps can highlight pathological features but cannot effectively indicate the absence of disease. Despite this initial increase in overdiagnosis, grader accuracy improved over time, suggesting that clinicians adapted to interpreting heatmaps with experience.³⁰

Moreover, although 7-field ETDRS group stereoscopic color fundus photography remains the gold standard for DR, its high cost and time demands have led to the use of handheld and smartphone-based cameras, especially in community-based screening initiatives. Regarding camera type, smartphone-based or portable fundus cameras demonstrated higher sensitivity than desktop fundus cameras. However, they exhibited a slight decrease in specificity, particularly for RDR detection. In our meta-analysis, camera type emerged as a significant source of heterogeneity, which suggested that hardware differences, including image quality and field of view, directly influence AI performance, especially in detecting more severe disease stages. These results align with those reported by Tan et al.³¹, who found a pooled sensitivity and specificity of 87% and 94% for any DR and 91% and 89% for RDR, respectively. However, while they observed a progressive increase in sensitivity and specificity as DR severity advanced (pooled sensitivity and specificity were 39% and 95% for mild NPDR, 71% and 95% for moderate NPDR, and 80% and 97% for PDR), our meta-analysis did not specifically assess the accuracy for each DR stage. Such an analysis was not possible due to differences in study methods, reference standards, and DR classification approaches.

Furthermore, we examined studies that specifically evaluated smartphone-based and handheld fundus imaging for DR detection to understand the impact of device type on diagnostic performance. Wintergerst et al.¹⁰ found that SBFI, especially when using indirect ophthalmoscopy, offered the highest-quality images, the widest field of view, and demonstrated excellent sensitivity and specificity (0.79-0.99 for any DR and 1.0-1.0 for severe DR), and excellent agreement with the reference standard (Cohen's kappa 0.868). Salongcay et al.¹¹ also reported that non-mydriatic and mydriatic handheld retinal imaging obtained good to excellent kappa agreement values with the ETDRS 7-standard field photography. However, the non-mydriatic method was linked to higher rates of ungradable images and lower levels of agreement.¹¹ Similarly, Prathiba et al.³² found that the non-mydriatic retinal camera demonstrated good agreement with standard tabletop fundus photography. Nevertheless, as with other non-mydriatic approaches, a higher proportion of ungradable images was observed, reinforcing the need for selective pupil dilation to improve image quality and reduce screening errors.³² These findings suggest that for community-based DR screening programs, device selection should consider the trade-off between portability, image quality, and the need for pupil dilation to optimize diagnostic accuracy and reduce false positives.

Although this review focuses on diagnostic accuracy, real-world factors like patient adherence are crucial for successful DR screening programs. The RAIDERS trial in Rwanda evaluated how AI-assisted screening influenced follow-up adherence. Mathenge et al.³³ found that immediate AI feedback increased referral adherence by 30.1% (51.5% vs. 39.6%, $p=0.048$) and a faster median time to follow-up (4 vs. 8 days) compared to human grading. Similarly, Liu et al.³⁴ reported a threefold improvement in adherence (55.4% vs. 18.7%) after implementing AI-based screening in a low-income primary care setting. These findings highlight the potential benefits of AI-assisted screening beyond its diagnostic performance. It also aligns with findings from public perception studies where patients demonstrated high confidence in AI-generated medical diagnoses, suggesting that trust in AI may positively influence screening adherence.³⁵ AI-based/assisted screening may also improve real-world patient engagement by reducing delays and enhancing adherence to follow-up care.

Expanding DR screening by task-shifting to non-ophthalmologists is an important strategy, especially in resource-limited settings where access to specialists is scarce. Two studies evaluated the diagnostic agreement between non-ophthalmologists (FPs/general physicians) and retinal specialists in DR screening. Cunha et al.¹² evaluated FP performance in DR screening, comparing it with retinal specialists. They found that FPs achieved moderate to substantial agreement with a retinal specialist ($k=0.56-0.73$), though agreement on macular edema was fair to moderate ($k=0.33-0.51$). However, similar agreement was also demonstrated between GOs and the retinal specialist, which suggests that FPs and GOs had similar diagnostic skills.¹²

Similarly, Piyasena et al.¹³ reported that general physicians achieved high agreement for any DR detection ($k=0.42-0.47$ in non-mydriatic imaging, improving to 0.66-0.68 in mydriatic imaging) and for RDR ($k=0.23-0.29$ non-mydriatic, improving to 0.68-0.76 mydriatic). However, the kappa agreement value for maculopathy detection was lower ($k=0.29$ non-mydriatic). The study also highlighted that ungradable images were high (43.4%) in non-mydriatic imaging but decreased to 12.8% after pupil dilation, reinforcing the importance of image quality for accurate DR screening.¹³ Both studies suggest that trained non-ophthalmologists can effectively detect RDR, but challenges remain in maculopathy detection and handling ungradable images. These findings underscore the need for further training and calibration of primary care providers if task-shifting strategies are to be effectively deployed in low-resource settings.

Our review has several strengths. One of the key strengths is its focus on DR screening in developing countries, where access to ophthalmologists is often limited. By including various screening modalities, such as AI-based/assisted identification, smartphone-based or portable fundus imaging, and trained non-ophthalmologist-assisted screening, this review incorporates a wider range of diagnostic methods, allowing for a broader comparison of different screening approaches and providing valuable insights into practical alternatives for resource-

limited settings. We also performed a meta-regression analysis incorporating multiple relevant factors, offering important insights. Additionally, most of the included studies reflect real-world screening conditions, enhancing the applicability of these findings to national DR screening programs and public health initiatives.

Nevertheless, this review has several limitations. First, the included studies cover a range of study designs, including retrospective, prospective, cross-sectional, and randomized controlled experiments. The heterogeneity in study design may introduce variability in the reported diagnostic performance of the AI models. Second, the meta-regression analysis identified camera type as a significant source of heterogeneity, suggesting that differences in imaging hardware, such as resolution and field of view, impact diagnostic accuracy. However, mydriatic status and AI algorithm type did not significantly contribute to heterogeneity, indicating that other unaccounted factors may still influence screening accuracy. Another limitation is the unequal distribution of studies across subgroups. Moreover, this meta-analysis focused primarily on diagnostic accuracy, without assessing whether earlier detection through AI-assisted or non-ophthalmologist screening improves patient outcomes such as treatment adherence and vision preservation.

Conclusion

This review highlights the growing feasibility of integrating AI-based and portable imaging technologies into DR screening programs in developing countries. Portable fundus cameras integrated with AI-based software can potentially lower the workload of ophthalmologists while reducing missed or incorrect diagnoses, ultimately helping to prevent vision loss caused by DR. Our findings suggest that both non-mydriatic and mydriatic imaging perform well, making them promising options for large-scale screening. However, pupil dilation should be considered for patients with ungradable retinal images to improve sensitivity without compromising specificity, as it can enhance image quality and reduce missed diagnoses. Ideally, this approach should be conducted under the supervision of trained physicians to maintain screening accuracy, reduce unnecessary referrals, and provide timely and appropriate care. These findings also emphasize the importance of quality assurance measures, including regular training, structured feedback loops, and possibly integrating AI decision support to assist non-specialist graders. Standardizing grading criteria, improving image quality, and refining AI models will be essential to developing reliable and scalable DR screening solutions, particularly in resource-limited settings. Our study demonstrated diagnostic accuracy across modalities, which can guide the development of more inclusive, scalable, and economical national screening programs. This insight might help policymakers choose the appropriate technologies based on workforce availability and local infrastructure. Future research to improve diagnostic performance should assess how these screening techniques could affect clinical outcomes including early intervention, treatment

adherence, and long-term vision preservation. These outcome-based studies are essential to fully demonstrate the public health benefits of integrating AI-assisted screening into routine diabetes care.

Ethics

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Declarations

Authorship Contributions

Surgical and Medical Practices: K.A.H., A.A., N.M.A.S., T.E., Concept: Y.Y., K.A.H., Design: Y.Y., K.A.H., Data Collection or Processing: Y.Y., A.C.V.G., N.P.K.M.D., Analysis or Interpretation: Y.Y., K.A.H., A.A., N.M.A.S., T.E., A.C.V.G., N.P.K.M.D., Literature Search: Y.Y., K.A.H., A.A., N.M.A.S., T.E., A.C.V.G., N.P.K.M.D., Writing: Y.Y., K.A.H.

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Complications of Periorbital Cosmetic Hyaluronic Acid Filler Injections: A Major Review

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Abstract

Hyaluronic acid (HA) filler injection is one of the most common methods for managing signs of aging in the periorbital area and is considered a safe and reversible procedure. The purpose of this review was to perform a comprehensive analysis of the incidence, risk factors, pathophysiology, signs and symptoms, and treatment methods of complications related to cosmetic periorbital HA filler injections, as well as review hyaluronidase indications, appropriate dosage, and safety measures. Complications were classified as immediate injection-related reactions (erythema, early edema, bruising/hematoma), early complications (loss of vision, acute infection, early contour irregularities, persistent edema), late complications (late edema, late contour irregularities), blue discoloration, xanthelasma palpebrarum, and filler in the orbit. Prospective and retrospective studies as well as case reports were reviewed. Immediate injection-related reactions such as erythema, edema, and bruising/hematoma were the most reported complications, followed by early contour irregularities and blue discoloration. Persistent and late edema and late contour irregularities were reported less frequently. These were mainly minor complications that were reversible through conservative management or hyaluronidase injection. Filler-related loss of vision, xanthelasma palpebrarum, and filler in the orbit were infrequent but potentially serious complications that could cause patients significant distress. These were mainly reported through case reports and case series. Urgent treatment with high dose hyaluronidase is necessary for successful management of injection-related vision loss. Physicians must have a thorough knowledge of orbital anatomy, the signs and symptoms of complications, and how to avoid them, and must be equipped to intervene immediately if necessary.

Keywords: Hyaluronic acid, complication, edema, nodules, blue discoloration, inflammation, infection, vision loss

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Introduction

Facial aging is characterized by three main components: volume loss, gravitational tissue descent, and deterioration of skin quality and laxity. The most common signs of aging in the periorbital region are the formation of tear troughs, prominent upper eyelid sulcus, brow descent, and wrinkles. All of these contribute to a “tired” and “old” appearance that leads individuals to seek rejuvenating treatments.¹ Hyaluronic acid (HA) is a hydrophilic material that can increase skin turgor and hydration. It activates dermal fibroblasts, stimulates collagen neogenesis, and acts as an anti-inflammatory agent in certain forms.² Injected HA can be degraded using hyaluronidase, providing patients and physicians with a sense of reversibility and safety.³ These properties make HA a near-ideal material, and injection of HA fillers is one of the most preferred rejuvenation methods.

There are various types of HA fillers with different rheologic properties, molecular weight, and crosslinking techniques, all produced for specific regions and indications.^{2,4} The elastic modulus (G') of an HA filler represents its capacity to return to its original form once a shearing stress is removed. A filler with higher G' is firmer, more resistant to tissue pressure, more durable, and has more lift power. The viscous modulus (G'') represents the resistance to dynamic forces. A filler with higher G'' has less liquid-like properties and is less prone to deform and flow when injected into tissue.^{5,6,7}

HA filler injection has been used in the periorbital area since the early 2000s and is generally regarded as a safe and effective method with high patient satisfaction.⁸ However, several complications ranging from minor injection site reactions to chronic edema and contour irregularities, filler migration, and rarely, vision loss can be encountered. While some complications are related to injection technique or filler properties, the exact



reason for others is yet to be understood.³ With the increasing popularity of filler injection, an increase in the rate of these adverse events is inevitable. The purpose of this paper was to report the frequency, findings, risk factors, and methods for prevention and treatment of complications related to cosmetic periorbital HA filler injections through a systematic review of retrospective and prospective studies and case reports. We also addressed hyaluronidase indications, appropriate dosage, and safety measures.

I. Immediate injection-related reactions: These are categorized as erythema, early edema, and bruising/hematoma.

Erythema

Erythema is reddening of the skin due to vasodilation triggered by a cutaneous inflammatory reaction to an irritant factor.⁹ It is usually mild and transient, with the highest reported rate being 40% in one study. Rates of erythema in various studies are presented in [Table 1](#).¹⁰⁻³⁶ Preexisting skin conditions like rosacea and certain injection techniques like serial needle injection are risk factors for erythema.^{27,37} Waiting 1 month after the treatment of dermatitis and up to 3 months after the treatment of active rosacea is recommended to avoid inflammatory reactions.³ Cold application, short-term steroid ointments, and vitamin K cream can be used to manage erythema.³⁷

Early Edema

Early edema can occur as reaction to skin and soft tissue trauma caused by injection, or due to a type 1 hypersensitivity reaction (HSR).

Injection-related early edema has been reported at rates of 0-100% ([Table 1](#)).¹⁰⁻³⁶ Needle injection and lower viscosity HA gels were associated with lower rates of edema.^{11,27,32} Avoiding frequent passes with needle, using ice packs before and after injection, and avoiding alcohol consumption for 12-24 hours before and after injection are beneficial measures.^{14,38} Using antihistamines for patients with known previous allergic reactions, mixing filler with triamcinolone or silicate creams, and preferring an upright sleeping position are other recommended precautions against injection-related edema.³⁹

Type 1 HSR (angioedema) should be kept in mind in cases of excessive bilateral generalized eyelid edema starting within minutes to hours after injection. Urticaria and itching may accompany. Medical treatment is via oral antihistaminics and corticosteroids. Patients should be monitored closely, as generalized symptoms involving the respiratory, gastrointestinal, or cardiovascular systems require hospitalization with intravenous treatment.^{3,40}

Bruising/Hematoma

Bruising and hematomas occur due to compromised vascular integrity. This complication is rather common, with rates of 0-100% in various studies ([Table 1](#)).¹⁰⁻³⁶ Using a 22-gauge or thinner cannula is reported to result in lower rates of bruising compared to needles.^{27,32} Marking the injection site beforehand,

avoiding frequent passes with the needle, and applying ice before and after injections are other beneficial measures.¹¹ A cardiology consultation should be requested for patients on anticoagulants to weigh the risks and benefits of discontinuation. As certain supplements such as garlic, hawthorn, ginkgo biloba, chondroitin-glucosamine, echinacea, aloe vera, and St. John's wort are shown to increase the risk of bleeding, physicians must take a detailed history of dietary supplements and advise patients to avoid these ingredients for 2 weeks prior to injection.⁴¹ Alcohol should be avoided for 12-24 hours before and after injection.^{11,14,38} Bruising is usually mild and disappears within a few days with conservative interventions such as ice packing.

II. Early complications: These are categorized as vision loss, acute infection, persistent edema, and early contour irregularities.

Vision Loss

1. Filler Embolization of Vascular Structures

Although rare, partial or complete loss of vision resulting from arterial occlusion after HA injection is one of the most devastating complications of fillers. None of the studies in this review reported vision loss. However, according to a recent review of 60 documented cases of filler-related vision loss between 2015 and 2018, the injection area was the brow in 3 (5%) of the cases and the tear trough in 1 (1.7%).⁴² Vision loss with or without pain usually occurs immediately, within minutes to hours, or up to a day in rare cases. Vision can range from no light perception to Snellen 0.7, depending on the scale of vascular involvement.⁴³ Nausea or vomiting, ophthalmoplegia, exotropia, ptosis, skin necrosis, and acute ischemic stroke may be among associated signs and symptoms.⁴²

The supratrochlear artery (STA), supraorbital artery (SOA), dorsal nasal artery (DNA), and angular artery (AA) are distal branches of the ophthalmic artery (OA). Inadvertent injection into these arteries can lead to retrograde embolization of the OA, central retinal artery, and choroidal arteries, or may cause posterior ischemic optic neuropathy, leading to vision loss.^{42,44} In the tear trough, the area between a line crossing the medial pupil and the lateral wall of the nose is described as a danger zone due to the presence of anastomoses of the nasal branch of the infraorbital artery to the STA, DNA, and AA.⁴⁵ Injection into the STA, SOA, and their branches is the main concern during superior sulcus and brow injections.⁴⁴

Excellent knowledge of anatomy and compliance with injection guidelines are important to avoid arterial embolization. Using blunt cannulas or small-bore needles and smaller syringes, withdrawing before injection, gentle and slow injection with multiple small boluses, and avoiding previously traumatized areas are among the suggested precautions.^{3,44} High frequency ultrasound is suggested as a potential tool to help avoid vascular complications during injection by simultaneously identifying injection planes and danger zones such as the infraorbital foramen.⁴⁶ Injection must stop as soon as the patient complains of pain or vision loss. Immediate injection of hyaluronidase is the main intervention technique.

Table 1. Characteristics and complication rates of studies of cosmetic hyaluronic acid filler injection in the periorbital area

Study	Treatment area	Filler agent/ method	Patient number	Follow-up*	Erythema	Bruising	Early edema	Early contour irregularity	Blue discoloration	Persistent edema	Late edema	Vision loss	Late contour irregularity
Goldberg et al. ¹⁰ , 2006	Infraorbital, eyebrow	Restylane/ suborbicularis	155	Up to 12 mo	0 (0%)	42 (27%)	18 (15%)	18 (15%)	12 (10%)	5 (3%)	0 (0%)	0 (0%)	0 (0%)
Morley et al. ¹¹ , 2009	Eye brow	Restylane/ preperiosteal	27	Mean 13 mo	0 (0%)	27 (100%)	27 (100%)	0 (0%)	N/A	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)
Beros ⁵³ , 2010	Infraorbital	Restylane/ preperiosteal	26	3 mo	0 (0%)	7 (13%)	12 (21%)	2 (14%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Choi et al. ¹³ , 2011	Upper eyelid/ superior sulcus	Restylane/ suborbicularis	7	Mean 9.6 (3-18) mo	0 (0%)	7 (100%)	7 (100%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Morley and Malhotra ¹⁴ , 2011	Infraorbital	Perlane/ suborbicularis	100	Mean 5.1 (1-18) mo	0 (0%)	75 (75%)	26 (26%)	33 (33%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Viana et al. ¹⁵ , 2011	Infraorbital	Restylane/ preperiosteal	25	Mean 9.5 (8-15) mo	10 (40%)	13 (52%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
De Pasquale et al. ¹⁶ , 2012	Infraorbital	Uma Jeunesse/ suborbicularis	22	36 mo	0 (0%)	4 (18.2%)	2 (9.1%)	6 (27.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Berguiga and Galatoire ¹⁷ , 2017	Infraorbital	Teosyal Puresense Redensity II/ suborbicularis	151	Up to 1 mo	7 (6%)	17 (11.3%)	22 (14.6%)	0 (0%)	4 (2.6%)	1 (0.9%)	N/A	0 (0%)	0 (0%)
Niforos et al. ¹⁸ , 2017	Infraorbital	Juvederm Vollbella-L/deep plane	80	Up to 12 mo	38%	39%	26%	33%	3 (4%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)
Mustak et al. ¹⁹ , 2018	Infraorbital, eyebrow	Restylane/ suborbicularis	147	Mean 6.3 (5-9) y	Not specified	Not specified	Not specified	Not specified	46 (31.3%)	17 (11.5%)	Not specified	0 (0%)	45 (30.5%)
Cho et al. ²⁰ , 2018	Infraorbital	Cleviel Fine/ <i>not specified</i>	9	24 wk	0 (0%)	1 (11%)	6 (66%)	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	0 (0%)
Hall et al. ²¹ , 2018	Infraorbital	Juvederm Voluma XC/suborbicularis	101	Mean 12 (4-17) mo	0 (0%)	10 (10%)	3 (3%)	2 (2%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
Hussain et al. ²² , 2018	Infraorbital	Juvederm Ultraplus XC/ suborbicularis	150	12 mo	6 (4%)	3 (2%)	12 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mustak et al. ²³ , 2018	Eye brow	Restylane-L/ ROOF	20	At least 5 y	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A	3 (15%)	0 (0%)	0 (0%)	0 (0%)
Romeo ⁵⁴ , 2019	Eye brow	Yvoire volume+/ ROOF	427	At least 12 mo	0 (0%)	0 (0%)	2 (0.4%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diwan et al. ²⁵ , 2020	Infraorbital	Teosyal Puresense Redensity II/ preperiosteal	24	4 wk	0 (0%)	1 (4.1%)	4 (16.6%)	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	N/A

Table 1. Continued													
Study	Treatment area	Filler agent/ method	Patient number	Follow-up*	Erythema	Bruising	Early edema	Early contour irregularity	Blue discoloration	Persistent edema	Late edema	Vision loss	Late contour irregularity
Fabi et al. ²⁶ , 2021	Infraorbital	Juvederm Volbella-L/ suborbicularis	103	12 mo	0 (0%)	4 (3.8%)	3 (2.9%)	0 (0%)	6 (5.8%)	0 (0%)	3 (2.9%)	0 (0%)	0 (0%)
Nanda et al. ²⁷ , 2021	Infraorbital	Crosslinked HA/ suborbicularis	60	12 mo	20 (33%)	5 (8.3%)	5 (8.3%)	4 (6.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Scarano et al. ²⁸ , 2021	Eyebrow	Crosslinked HA/ ROOF	15	6 mo	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Shah- Desai and Joganathan ²⁹ , 2021	Infraorbital	Restylane Vital Light/subdermal	165	Mdn 6 (6-36) mo	0 (0%)	100 (60.6%)	2 (1.2%)	0 (0%)	3 (1.8%)	2 (1.2%)	0 (0%)	0 (0%)	0 (0%)
Vadara et al. ³⁰ , 2021	Infraorbital	Juvederm Volbella/ subdermal	15	24 mo	0 (0%)	4 (26.6%)	0 (0%)	0 (0%)	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Juvederm Voluma/ suprapariosteal	15	24 mo	0 (0%)	1 (6.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wollina and Goldman ³¹ , 2021	Infraorbital	Belotero suprapariosteal	45	-	0 (0%)	4 (8.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diaspro et al. ³² , 2022	Infraorbital	Teosyal PureSense Redensity II/ suborbicularis	600	Mean 12 (4-17) mo	14 (2.3%)	6 (1%)	16 (2.6%)	0 (0%)	27 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lee et al. ³³ , 2022	Infraorbital, crow's feet	Yvoire-Hydro/ intra dermal	27	28 wk	1 (3.7%)	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Can and Betül Gözel ³⁴ , 2022	Upper eyelid	Low- viscosity HA/ suprapariosteal	25	Mdn 14 mo	0 (0%)	0 (0%)	25 (100%)	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Biesman et al. ³⁵ , 2024	Infraorbital	Restylane Eyelight/ suprapariosteal	287	12 mo	0 (0%)	5 (1.6%)	12 (3.8%)	4 (1.3%)	1 (0.3%)	4 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Fakih- Gomez et al. ³⁶ , 2024	Infraorbital	CPM-B/ retroseptal/ suprapariosteal	198	-	0 (0%)	1 (0.5%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

^a Follow-up times given in weeks (wk), months (mo), or years (y), with mean or median (med) and range in parentheses when available. HA: Hyaluronic acid; ROOF: Retro-orbicularis oculi fat; N/A: Not applicable.

*Follow-up times given in weeks (wk), months (mo), or years (y), with mean or median (med) and range in parentheses when available. HA: Hyaluronic acid, ROOF: Retro-orbicularis oculi fat, N/A: Not applicable

The hyaluronidase dose reported in studies varies between 500 and 3000 IU, and reported injection sites are subcutaneous, retrobulbar, the infraorbital foramen, the supratrochlear and supraorbital notches, and intraarterial to the OA.^{42,47} Early injection and degree of initial vision loss are considered the most important factors for treatment success. Still, 50% success within minutes was reported for hyaluronidase injection. Ocular massage, hyperbaric oxygen, intravenous steroid or mannitol, acetazolamide, and antiplatelet agents are among the various documented interventions.^{3,40,42,44}

2. Globe Perforation

Inadvertent globe perforation and intraocular filler injection is another rare cause of filler-related vision loss, with two reported cases in the literature. One study reported a case where filler was injected into the anterior chamber via a lamellar corneal perforation,⁴⁸ and another reported intravitreal HA injection accompanied by retinal hole and small localized vitreous hemorrhage.⁴⁹ In both patients, symptoms included dull pain, chemosis, and blurred vision. No intraocular infection or significant inflammation was seen in either case. In the first case, HA was removed via irrigation and aspiration, leading to complete recovery.⁴⁸ In the latter case, the retinal hole was treated with laser photocoagulation and the HA was left in the vitreous under close observation, with no further complications other than cloudy vision at 2-months follow-up.⁴⁹

To avoid this problem, all injections must be performed by licensed and well-trained practitioners. Conformers may be used to protect the cornea when injection is performed by inexperienced physicians or during cases with risk factors such as degenerative myopia or thyroid eye disease. Physicians must be able to recognize the signs and symptoms and be prepared to either intervene immediately, or refer the patient to an adequate ophthalmological center urgently.⁴⁸

Acute Infection

Infection/cellulitis of the eyelid skin is rare. The reported incidence is 0.04% to 0.7%.^{50,51} Acute infection presents as persistent edema accompanied by erythema, fluctuance, pain, and occasionally nodules.⁵² The most common causative agents are *Staphylococcus aureus* and *Streptococcus pyogenes*. However, atypical bacteria should be suspected in cases occurring later than 2 weeks after injection.⁴⁰ Staphylococcal cellulitis may be accompanied by abscess formation.⁵⁰ Physicians should comply with the rules of sterile injection, and patients should be properly informed about postinterventional care to minimize the risk.³ Amoxicillin-clavulanate or clindamycin are recommended empiric antibiotics for first-line treatment. Topical antibiotics can be utilized in conjunction with systemic therapy. Abscesses should be drained and cultured to test antibiotic sensitivity. Patients should be monitored for systemic findings and admitted to hospital if necessary.⁴⁰

Herpes simplex reactivation is another complication that physicians must be aware of, although this occurs more commonly after lip injections. Patients present with typical herpetic vesicles and lymphadenopathy. Systemic antiviral therapy should be started promptly in such cases.⁴⁰

Acute conjunctivitis was reported in one patient of a series that included 24 upper eyelid injections. In this case, conjunctivitis was caused by inadvertent injection of filler into the bulbar conjunctiva and was treated by surgical removal.⁵⁰

Early Contour Irregularities

Early contour irregularities occur due to clumps of non-homogeneously dispersed fillers and can be seen in up to 33% of patients (Table 1).¹⁰⁻³⁶ Thin eyelid skin and lack of subcutaneous fat tissue in the infraorbital region contribute to the aesthetically displeasing nature of this complication. Overcorrection, superficial placement,⁴⁰ and fillers with higher G' and G'' values are reported risk factors.^{10,14,53} Deep preperiosteal injections, using fillers with lower G' and G'' values,⁵ and massaging afterwards are the main methods of minimizing irregularities while maintaining sufficient volume restoration. Shah-Desai and Joganathan²⁹ reported subdermal microdroplet injection of very low G' and G'' materials with a 0% rate of contour irregularities and proposed this method for infraorbital injection in younger patients who require less volume restoration.

When encountered, treatment options include massage and additional HA injections to smoothen the appearance of the area. Dissolving the filler with hyaluronidase is effective for cases that do not respond to conservative management.⁴⁰ Dosage varies according to the filler material and extent of nodules, and doses of 5 to 150 units have been reported.⁵⁴

Persistent Edema

Persistent edema starts within days after injection and persists for more than 4 weeks despite conservative management.^{23,55,56} Its prevalence varies between 0% and 15% (Table 1).¹⁰⁻³⁶ It is non-inflammatory and non-erythematous, with a soft, pale appearance that may resemble fluid sacs. In the infraorbital area it extends beyond the borders of the injection site through the malar eminence, which is often referred to as malar edema.¹⁰ On the upper eyelids it can present as puffiness around the eyes or pale edema of the upper eyelids and brow area without inflammatory findings.^{23,55}

In the infraorbital region, edema is thought to occur due to accumulation of filler and extracellular fluid superficial to the malar septum. The malar septum is a fibrous barrier that starts at the level of the inferior orbital rim and inserts into the cheek skin approximately 3 mm below the lateral canthus, at the level of the inferior border of the orbicularis oculi muscle. It divides the suborbicularis oculi fat into superior and inferior compartments. Its relative impermeability leads to accumulation of edema within the superiorly located structures. Injection

superficial to this landmark may cause edematous accumulation, exacerbated by compression of periorbital lymphatic flow by the filler material. Hydrophilic fillers with high water uptake, such as those crosslinked with Hyalocross technology, can also lead to higher rates of persistent edema.^{5,39,52}

Older age, skin laxity, associated skin problems (allergies, rosacea), preexisting malar mounds, and herniated fat pads are patient-related risk factors.^{3,10}

Obtaining a detailed patient history and careful physical examination and patient selection are important steps to avoid persistent edema. Performing consecutive injections less frequently, using lower volumes, and opting for deep preperiosteal injections can decrease the risk of persistent edema.^{17,56} However, the level of the initial injection may not always correspond to the final localization of the filler, as anterior migration can occur based on anatomical variances and filler properties.⁵⁷

Upon encountering persistent edema, physicians should look for any accompanying sign of inflammation such as redness, tenderness, and nodules to rule out infection or delayed inflammatory reactions.⁴⁰

Close follow-up with ice packing, elevating the head at night, and periorbital massage to increase lymphatic drainage may be effective for treatment.^{29,40} Topical treatment includes cortisone creams, silicate creams, and triamcinolone injections.³⁹ Hyaluronidase injection of 10-50 units is usually effective in cases not responsive to conservative treatment.^{10,51,56} Nevertheless, some cases may not completely resolve with hyaluronidase, and cases requiring up to 750 units over multiple sessions are reported in the literature.^{10,39,52}

III. Late complications: These are categorized as late edema and late contour irregularities.

Late Edema

Late edema appears 1 month to years after injection.^{11,58,59,60} Although the exact prevalence is unknown, studies show that it may occur in up to 5% of cases before the end of 12-month follow-up.^{11,18} It can affect both the upper and lower eyelids. In a study of 78 patients with late periorbital edema, 17 cases involved upper eyelids while 61 involved lower eyelids.⁶¹ Late edema of the upper eyelids may present as superomedial edema, centrolateral brow edema, or upper lid edema with ptosis.⁶¹ In the lower eyelids, it presents as late chronic edema that may be accompanied by the Tyndall effect and may worsen over time.⁶² There is no accompanying signs of inflammation such as redness, tenderness, or nodules.^{19,59,63}

The underlying mechanism is a subject of debate. Dubinsky-Pertsov et al.⁶¹ and Skippen et al.⁶² proposed that the main mechanism was HA incarceration within the orbicularis oculi fibers leading to muscle degeneration. Histologic studies show that HA in the human body is not always completely degraded by natural processes, and some material can remain within tissues even several years after injection. This leads to degeneration of the orbicularis oculi fibers, which are then surrounded by

pools of excess extracellular matrix.⁶⁰ Furthermore, they argued that HA is a hydrophilic material that undergoes isovolumetric degradation in which each particle interacts with water as the filler breaks down, thus preserving the total volume. This process, along with a reduction in orbicularis oculi contractile function which would normally aid in lymphatic fluid flow, may lead to edema even years after injection.^{61,62} More hydrophilic materials such as Hyalocross and Vycross family fillers may be more prone to cause late edema.⁵²

When encountering a case of periocular edema, it is important to be highly suspicious of and persistently question for a history of fillers. Patients may be reluctant to admit to or forget getting filler injections.⁵² Late non-inflammatory periorbital edema should be differentiated from delayed HSR, where edema is associated with induration, nodules, and other inflammatory findings.⁶⁴

Hyaluronidase is reported to be sufficient for resolution of late edema even in cases that last several years. Dosage depends on the extend of edema and varies between 30 and 90 units.^{61,62}

Late Contour Irregularities

Late contour irregularities may present as palpable masses or nodules, with or without accompanying edema and inflammation, weeks to months after injection.³ The incidence is unclear because most studies had short-term follow-up, and our knowledge about this complication is mainly from case reports or series. Mustak et al.¹⁹ reported a frequency of 30.5% in their series of patients with at least 5-year follow-up, with most cases being mild irregularities not requiring intervention. Late irregularities may be attributed to non-inflammatory mechanisms such as filler capsule contraction⁶⁵ or to delayed inflammatory reactions that include foreign body granuloma, biofilms, atypical infectious granuloma, and delayed type 4 HSR.⁶⁴

Non-inflammatory late nodules are infrequent. They present as firm masses with clear borders and no inflammatory findings. Microscopic examination shows encapsulated Alcian blue-staining HA with no surrounding inflammatory cells. They are usually resolved by surgical excision of the mass.^{65,66}

Inflammatory nodules are accompanied by erythematous edema and tenderness.^{67,68,69} The exact etiology may be difficult to identify with only clinical findings and skin sensitivity tests, and histopathological examination of biopsy material, tissue cultures, and polymerase chain reaction tests may be required for definitive diagnosis.^{4,64} In a histopathological study of nodules after various types of filler injections, granuloma due to foreign body reaction and atypical infectious granuloma were reported as the most common etiologies.⁷⁰

Foreign body granuloma occurs due to chronic activation of macrophages and lymphocytes around a foreign object that cannot be removed via enzymatic degradation or phagocytosis.^{64,70} Histopathology reveals histiocytes and multinucleated giant cells surrounded by lymphocytes and eosinophiles.^{67,68} Crosslinked filler agents are more resistant to

enzymatic degradation and may be more prone to cause foreign body granulomas,⁴ although there is no definitive conclusion in the literature due to data scarcity and lack of a detailed filler history in these cases. Immune system reactivity or previous viral infections may also play a role.^{4,40}

Biofilms are caused by contamination of filler with skin microbiota such as *S. aureus* and *Cutibacterium acnes*. A biofilm consists of microbial cells and an extracellular polymeric substance. In time, biofilms may trigger a continuous immune response and lead to granulomatous inflammation and late nodules.^{3,4,40}

Atypical infectious granuloma presents as suppurative or caseating granuloma with central caseation necrosis and prominent neutrophilic infiltrate on microscopy. Mycobacterial infection with *Mycobacterium fortuitum* and *Mycobacterium marinum* has been reported as the main cause.⁷⁰ Infection can also be caused by a combination of various microbiologic agents such as fungal infection combined with *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus epidermidis*, or various inflammatory mechanisms may be present at the same time.⁶⁹

Delayed type 4 HSR is a cellular immune response to filler. Its general incidence after HA injections of all body parts is estimated to be 0.06%.⁶⁴ Although the immunogenicity of HA fillers is very low, HSR can still be triggered by many factors including molecular weight, additives, and the technology of HA production. Low-molecular-weight fillers are known to have proinflammatory properties. Crosslinking may also increase the immunogenicity of a filler by altering the natural configuration of HA.⁴ Vycross family fillers are associated with higher rates of late-onset inflammatory nodules compared to other materials.⁷¹

Avoiding uncertified filler materials and complying with the rules of sterile injection are important steps to avoid atypical infections and biofilm formation.⁴⁰ Skin testing 3-4 weeks prior to injection can rule out any sensitivity to agents that could cause delayed HSR. If skin testing reveals sensitivity to a certain ingredient, a different material should be preferred.⁶⁴ Medical treatment and degradation of the filler with hyaluronidase is the main treatment. There is no uniform algorithm for the dosage of hyaluronidase, and doses ranging from 30 to 300 units in total to 500 units every 48 hours have been reported.⁵⁴ In cases of granulomatous inflammation, oral antibiotics should be added to reduce the risk of spreading the biofilm and infection. Lincosamides, macrolides, and tetracyclines are among the suggested antibiotic agents. The presence of type 4 HSR warrants the use of oral or intralesional corticosteroids. Some authors suggest using a combination of antibiotics and corticosteroids because it is difficult to differentiate infectious etiology from HSR in most cases.^{3,4,40}

IV. Blue Discoloration (Tyndall Effect)

Blue discoloration is a well-known phenomenon that occurs after infraorbital HA injections. It can be observed weeks, months, or years after injection.⁵² Its incidence varies between

0% and 31%, and higher rates are reported in studies with longer follow-up (Table 1).¹⁰⁻³⁷ It is often referred to as the Tyndall effect, a phenomenon that occurs due to dispersion of light from superficially located filler under the thin and translucent lower eyelid skin.⁷² However, some authors challenge this term and suggest that the light is not scattered by the filler itself, but by colloidal material within superficial edema, especially in cases where blue discoloration occurs months to years after injection.^{39,73}

Many factors are related to blue discoloration, including injection location, use of needle vs. cannula, rheological properties, and crosslinking technology.

Injecting into the suborbicular or supraperiosteal plane leads to lower rates of blue discoloration.^{17,26} Diaspro et al.³² stated that needle injection is superior to cannula because it allows placement of single bolus of filler into the desired deeper location, whereas a cannula is more prone to result in superior misplacement. If the physician opts for a cannula, injecting multiple small boluses and firmly massaging the area are recommended.

The G' and G'' values of the filler may also play a role in the development of blue discoloration. Fillers with lower G' and G'' values are reported to be less likely to cause blue discoloration despite more superior injections.⁷⁴ However, Vadera et al.³⁰ conducted a study where they compared a lower G' filler injected subdermally at the medial, central, and lateral infraorbital area to a higher G' filler injected in the deep supraperiosteal plane at the lateral and inferolateral periorbital rim. They concluded that the latter technique led to a dramatic decrease in blue discoloration, required less filler volume, and had a longer-lasting effect.

On the other hand, recent studies using fillers with very low G' and G'' values, marketed as “skin boosters”, or fillers that contain non-crosslinked HA suggest that these products can be applied subdermally or intradermally with blue discoloration rates as low as 0-1.8%. Still, it must be kept in mind that these products have less volume-enhancing qualities and mainly target superficial wrinkles.^{29,33}

Crosslinking technology may also play a role in blue discoloration. It is recommended to refrain from injecting Hyalocross fillers superficially despite their lower G' and G'' because they are more hydrophilic and tend to bind more water and may cause more prominent blue discoloration.^{39,52} However, Hussain et al.²² reported no blue discoloration with a filler from the Hyalocross family. Vycross family fillers were also noted to cause blue discoloration more frequently.⁵²

Hyaluronidase injection is usually sufficient for treatment. The required dose may vary according to filler material and volume, and doses of 30-75 units have been reported.⁷⁵

V. Xanthelasma Palpebrarum

Xanthelasma or xanthelasma-like lesions on the eyelids after HA filler injection are rare, with only six reported incidences in the literature.^{76,77,78,79} All the cases were located on the lower eyelids and appeared as yellowish plaques around

the injected area a few weeks to months after injection. Examination usually reveals no significant hyperlipidemia. Histopathological examinations reveal foamy histiocytes filled with lipid droplets, macrophages containing material suggestive of HA fragments, and extracellular lipids in the superficial dermis.^{76,77} Although the exact mechanism is not known, binding of filler with extravasated low-density lipoprotein in tissues leading to phagocytosis by macrophages is considered a possible mechanism.⁷⁶ Hyaluronidase injection, steroid injection, fluorouracil (5-FU) injection, ablative or fractionated carbon dioxide laser, erbium-doped yttrium aluminum garnet laser ablation, or surgical excision are reported as plausible treatment approaches.^{76,77,78,79}

VI. Filler in the Orbit

Filler in the orbit is a rare complication that can occur due to inadvertent penetration of the orbital septum during injection,^{80,81,82} or migration of filler material into the orbit.⁸³

Inadvertent penetration of the septum may result in filler placement within the orbital fat pad or around the extraocular muscles. This can cause further bulging of the orbital fat pad and worsen the patient's appearance,⁸¹ cause myositis of the periorcular muscles,⁸⁰ or lead to sight-threatening retrobulbar hemorrhage if orbital vessels are perforated.⁸² Herniated fat pads, orbital rim thinning, and orbital septum weakening are among the risk factors for inadvertent septal perforation. Although preperiosteal needle injection is associated with higher risk, cannula injections can also lead to filler placement within the orbital fat pad.⁸¹ Surgical removal or degradation with hyaluronidase are treatment methods. Lateral canthotomy and cantholysis is required if orbital compartment syndrome occurs.⁸²

Migration of filler into the orbit can occur after filler injection to the periorbital area or various facial areas such as the glabella, temples, zygoma, midface, or nasolabial folds.⁸⁴ The most common symptoms are periorbital edema and a palpable mass that may appear months or years after injection. Inflammation and fibrosis within the orbit can lead to palsy of the intraorbital nerves, such as partial third nerve palsy leading to adduction deficiency.⁸⁴ The inferior oblique muscle is located near the orbital fat and capsulopalpebral fascia. Filler materials migrating around it can cause delayed HSR or foreign body reaction and subsequent inflammation of the muscle, leading to vertical diplopia.⁸⁰ Migration into the nasolacrimal sac can cause nasolacrimal obstruction.⁸⁴ Forceful injection of high amounts of filler and vigorous massaging are among the proposed causes of filler migration.⁸⁵

Diagnosis based on clinical history alone may not be possible in many cases. Orbital imaging via computed tomography or magnetic resonance imaging is useful to determine the location of filler or filler-related inflammation. Orbitotomy and histopathological examination is performed for definitive diagnosis.⁸⁴ Treatment is via surgical excision of the filler, degradation using hyaluronidase, or a combination of both.⁸⁴

Intraorbital injection of up to 120 IU hyaluronidase is reported to be safe and effective.

Mechanisms and Safety of Hyaluronidase for the Treatment of Hyaluronic Acid Filler-related Complications

Hyaluronidase is the main agent in the treatment of many HA filler complications. The required dosage varies depending on injection site, filler type, and amount of filler. Fillers with higher HA concentration and greater degree of crosslinking require higher doses of hyaluronidase.⁸⁶

Although hyaluronidase administration is generally regarded as a safe procedure, physicians should be aware of potential HSRs such as local cutaneous reactions (0.05-0.69%), urticaria and angioedema (<0.1%), and anaphylaxis, which is rare. An intradermal sensitivity test is recommended prior to elective injections. Concomitant use of non-steroidal anti-inflammatory drugs, aspirin, and vitamin C may decrease the efficacy of hyaluronidase.^{3,40}

Conclusion

In this paper, we provided a detailed review of the literature on complications of cosmetic periorbital HA filler injections. The reviewed papers present heterogeneous information, as the authors used different fillers and described various injection techniques and locations. Furthermore, heterogeneous terminology was used to describe similar complications. Some studies had small cohorts and short follow-up times that may not accurately reflect the incidence of long-term complications. Less common complications that develop months to years after injection were reported only in case reports.

Most complications associated with periorbital HA filler injection are mild-to-moderate immediate injection-related complications that are usually managed with conservative methods. Early contour irregularities, persistent edema, and blue discoloration are less frequent. Careful patient selection, avoiding highly hydrophilic materials, and injecting in the preperiosteal plane are important precautions. Hyaluronidase is usually effective as treatment. Acute infection is infrequent in the periorbital region, and late-onset atypical infections usually present as late-onset nodules. Knowledge is limited regarding the incidence and pathomechanisms of certain complications such as xanthelasma palpebrarum, late-onset edema, late contour irregularities, and filler in the orbit. Future studies with longer follow-up are necessary to acquire more information about these complications. Filler-related vision loss is a rare but devastating complication which is usually preventable by avoiding danger zones and injecting meticulously. Early diagnosis and prompt intervention are the most important factors for recovery.

Physicians should be thoroughly trained on the anatomy of the periorcular area, the rheological properties of fillers and correct injection methods, the warning signs and symptoms of possible serious complications, methods for avoiding complications, and proper management techniques.

Declarations

Authorship Contributions

Concept: M.B.H., H.N.B., Design: M.B.H., H.N.B., Data Collection or Processing: H.N.B., Analysis or Interpretation: H.N.B., M.B.H., Literature Search: H.N.B., Writing: H.N.B., M.B.H.

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New Phenotype in Two Siblings with Familial *FLVCR1* Mutation: Neurotrophic Keratopathy

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Abstract

The feline leukemia virus subgroup C receptor (*FLVCR1*) gene plays a role in heme, choline, and ethanolamine transport. In biallelic pathogenic *FLVCR1* variants, macrocytic anemia may be associated with childhood- or adult-onset neurodegeneration of the retina, spinal cord, and peripheral nervous system. In patients with *FLVCR1* variants, optic atrophy and retinitis pigmentosa are previously described ocular findings, but neurotrophic keratopathy has not been reported. In this study, we describe two patients with homozygous novel likely pathogenic variants in terms of their clinical findings, including neurotrophic keratopathy. On examination, the 2-year-old sister had bilateral central corneal clouding, leukoma, absent corneal reflexes, normal fundus findings, and protruding ears. The 5-year-old sister exhibited significant bilateral corneal leukoma and scarring, optic disc pallor, absent corneal reflexes, and autoamputation-like defects on the fingertips of both hands. Next-generation sequencing analysis of the 5-year-old patient revealed a homozygous likely pathogenic c.160dup p.Arg54ProfsTer36 variant of the *FLVCR1* gene that was not listed in the GnomAD, ESP6500, ExAC, or Clinvar databases. *FLVCR1* mutations can disrupt choline transport and therefore acetylcholine production. Acetylcholine increases cGMP in the cornea, promoting epithelial growth. A lack of this neurotransmitter in the cornea leads to epithelial destruction. The development of neurotrophic keratopathy in this patient and her sibling may be a new phenotypic feature of this novel variant.

Keywords: *FLVCR1*, neurotrophic keratopathy, neuropathy, optic atrophy

Introduction

The feline leukemia virus subgroup C receptor (*FLVCR*) gene plays a role in the transport of heme, choline, and ethanolamine. Biallelic pathogenic *FLVCR1* variants have been associated with NEDMISH (neurodevelopmental disorder with microcephaly, absent speech, and hypotonia) syndrome, which is characterized by macrocytic anemia, childhood- or adult-onset neurodegeneration of the retina, spinal cord, and peripheral nervous system, as well as a milder phenotype called retinopathy-sensory neuropathy syndrome.¹ Ocular pathologies such as optic atrophy or retinitis pigmentosa have been reported in both syndromes.^{2,3} In this study, we describe clinical findings including neurotrophic keratopathy in two homozygous carriers of a novel, likely pathogenic variant.

Case Reports

Two sisters, 2 and 5 years of age, presented to the ophthalmology outpatient clinic with complaints of whiteness in the eyes. The patients' parents were cousins. Despite an unremarkable prenatal history, both patients were being followed for global developmental delay and had reportedly never achieved the key milestones of sitting, walking, or speaking. They exhibited marked hypotonia and the parents reported multiple hospitalizations due to frequent infection. As the patients had no pain perception, they had widespread skin ulcers and scars on the tongue and fingers.

On physical and ophthalmologic examination, the 2-year-old girl exhibited leukoma in both corneas and protruding ears ([Figure 1](#)). There was no epithelial involvement in corneal fluorescein staining, the fundus was normal ([Figure 2](#)), and corneal reflex could not be elicited. The 5-year-old girl had significant leukoma and scarring in both corneas ([Figure 3](#)), corneal fluorescein staining revealed unilateral epithelial

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involvement, bilateral optic disc pallor (Figure 4), and corneal reflex could not be elicited. Partial auto-amputation of the finger tips was observed in both hands (Figure 5). The demographic and clinical characteristics of the cases are summarized in Table 1. The 5-year-old girl died 8 months later. The family history included two other girls with similar clinical complaints who had died previously.

Next-generation sequencing analysis in the 5-year-old patient revealed a homozygous likely pathogenic *FLVCR1* variant (c.160dup p.Arg54ProfsTer36) that was not reported in the databases. For molecular analysis, 2 mL of peripheral blood was collected in EDTA tubes and stored at -20 °C. Genomic DNA was isolated from peripheral blood leukocytes using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocols. All coding exons and exon-intron boundaries of 4,493 genes were amplified using the Clinical Exome Solution v2 kit (SOPHiA Genetics, Boston USA). The prepared library was sequenced on the Illumina NextSeq platform (Illumina Inc., San Diego, CA, USA). Together with clinical findings, the data were analyzed using Sophia DDM data analysis software (Sophia Genetics, Boston USA) (Figure 6).

Discussion

FLVCR1 gene variants exhibit a broad and pleiotropic phenotypic spectrum, ranging from adult neurodegeneration to

severe developmental disorders with variable anemia and skeletal malformations. Different phenotypes of this rarely reported gene defect have been recognized over time, and the genetic tests performed vary according to the phenotype.

FLVCR1 gene mutations can disrupt transport of choline, which plays an important role in methyl group metabolism

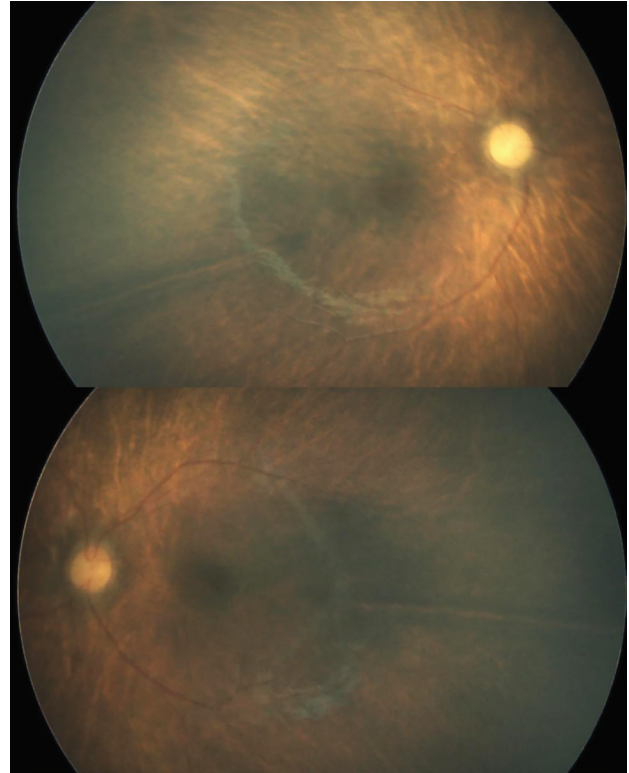


Figure 2. The 2-year-old female patient, normal fundus appearance



Figure 1. The 2-year-old female patient, corneal leukoma and protruding ears



Figure 3. The 5-year-old female patient, significant leukoma and corneal scar

and the synthesis of phosphatidylcholine and acetylcholine via the Kennedy pathway. Choline is essential for normal neurodevelopment.⁴ Maternal choline deficiency has been reported to impair hippocampal development and neuronal and retinal progenitor cell proliferation and differentiation in mouse embryos.^{5,6} Ethanolamine cannot be synthesized by humans and is a precursor to phosphatidylethanolamine synthesis via the Kennedy pathway.⁷ Phosphatidylethanolamine and



Figure 4. The 5-year-old female patient, defects in the fingertips

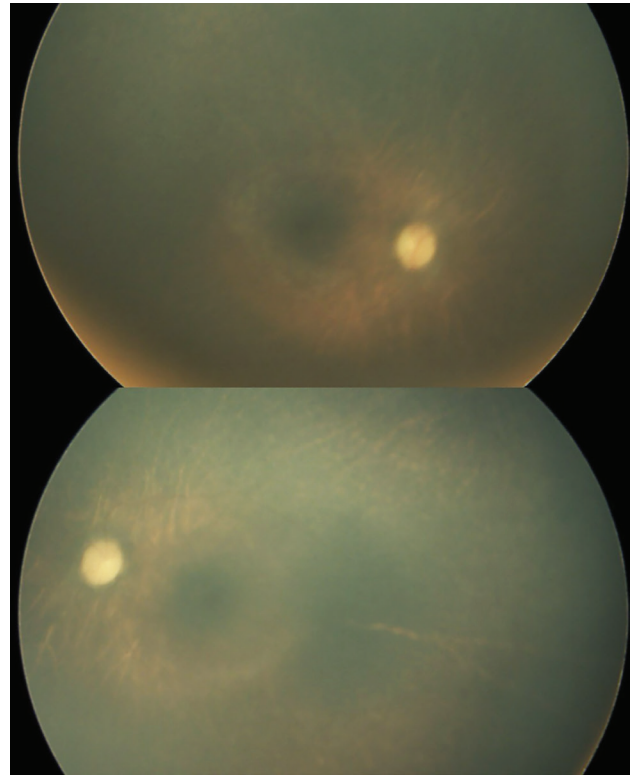


Figure 5. Five-year-old female patient, bilateral optic atrophy

phosphatidylcholine are membrane phospholipids required for membrane integrity, cell division, and mitochondrial respiratory function. These molecules are vital and their deficiency results in early death.

Damage to the dense corneal nerve endings from the long posterior ciliary nerves play a fundamental role in the pathophysiology of keratopathy. Studies have shown that these sensory neurons directly affect the integrity of the corneal

Table 1. Demographic and clinical characteristics		
	Patient 1	Patient 2
Age (years)	2	5
Sex	Female	Female
Corneal findings	Bilateral leukoma	Bilateral leukoma, left scar
Fluorescein staining	None	Left +
Corneal reflex	Absent	Absent
Fundus	Normal	Bilateral optic disc pallor
Additional findings	Protruding ears	Autoamputation of digits

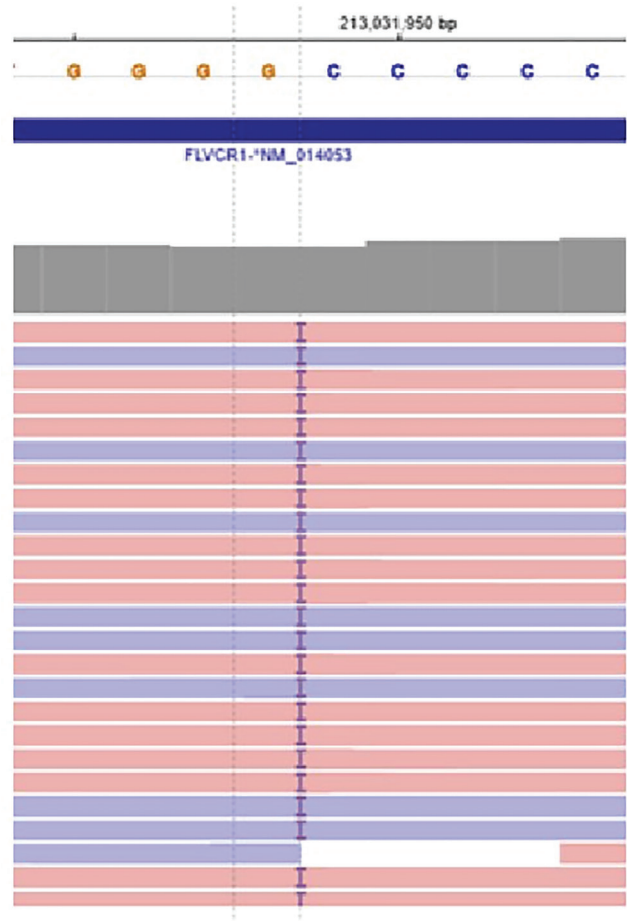


Figure 6. Integrated genomic imager variant visualization

epithelium. In the presence of neuronal destruction, the epithelial cells swell, lose their microvilli, and produce abnormal basal laminae. This can slow or stop mitosis, leading to epithelial defects.⁸ Although Cochet-Bonnet esthesiometer and in vivo confocal microscopy can be used for the objective assessment of corneal neuropathy, these could not be performed in our cases because they were not available in our clinic and the patients were not cooperative. However, these tests are recommended in similar cases.

Disrupted choline transport due to *FLVCR1* mutation results in inability to produce acetylcholine. The presence of this neurotransmitter in the cornea increases cGMP and promotes epithelial growth, whereas its deficiency leads to epithelial destruction, resulting in keratopathy. Microtrauma, infection, nerve damage, and various other factors inhibit cell mitosis, leading to recurrent epithelial erosion and ulceration. Loss of the corneal epithelial barrier leads to the development of stromal edema in areas of epithelial erosion.⁸

Our patient was found to carry a homozygous p.Arg54ProfsTer36 variant, which was not previously reported in the GnomAD, ESP6500, ExAC and Clinvar databases. These cases are distinguished from retinopathy-sensory neuropathy by the absence of retinitis pigmentosa and ataxia. Considering that *FLVCR1*-associated phenotypes arise from loss-of-function mutations, the frameshift nature of the novel variant identified in our patient evaluated in the context of the clinical findings support its classification as likely pathogenic. The development of neurotrophic keratopathy in this patient and her sibling may be a new phenotypic feature of this novel variant.

Genetic testing to identify specific causative pathogenic variants is important to confirm the diagnosis and provide appropriate genetic counseling to affected families. Identifying specific genetic defects allows for predictive testing of at-risk relatives and enables informed decisions about surveillance and preventive measures.

Ethics

Informed Consent: Written consent was obtained from the parent of the patients.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.D.K., M.F.A., H.P., Concept: B.D.K., M.F.A., H.P., Design: B.D.K., M.F.A., H.P., Data Collection or Processing: B.D.K., M.F.A., H.P., Analysis or Interpretation: B.D.K., M.F.A., H.P., Literature Search: B.D.K., M.F.A., H.P., Writing: B.D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Sustainability in Ophthalmology: A Proposal for the Digitalization and Recycling Promotion of Ophthalmological Drugs and Medical Devices

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Dear Editor,

Topical eye drops are among the most commonly prescribed treatments in ophthalmology practice. They are usually supplied to patients in a cardboard box with a printed package insert (also referred to as patient information leaflet). However, this traditional packaging method not only causes significant paper consumption in terms of environmental sustainability, but also limits information access because information leaflets quickly become outdated. Sustainability in health care has become increasingly important in recent years, with the reduction of unnecessary packaging in the health industry listed as an important goal in World Health Organization reports and the strategic plans of other international health organizations.¹ Medical studies have also emphasized the critical role of the pharmaceutical industry in reducing the carbon footprint of health services.² Given the extensive use of eye drops in ophthalmology, it is clear that even small changes in this area can significantly reduce the environmental impact. In this context, a

practical and feasible solution may be to eliminate the cardboard box and provide eye drops in bottles printed with a QR code link to a digital version of the package insert. Such an approach would:

1. Lighten the environmental burden by reducing paper consumption,
2. Facilitate timely updates of digital patient information leaflets,
3. Decrease logistic and printing costs for pharmaceutical manufacturers, and
4. Allow patients to access the most up-to-date information from a smartphone or computer via the QR code.

In addition, the ability to present digital information leaflets in accessible formats (e.g. as audio or large print) could offer significant convenience for older or visually impaired patients. This would have positive impacts on both environmental sustainability and patient experience and treatment adherence.³ Of course, such a transition requires the cooperation of the pharmaceutical industry and regulatory authorities. Providing a printed information leaflet is currently mandated by legal regulations, which may constitute an obstacle to the implementation of this practice. However, it is important to open discussions about such innovative practices today, as the trend toward digitalization in health care continues. Similar digital solutions are becoming increasingly common in prescribing processes in Europe and some other countries.^{4,5} Sustainability is a current topic in ophthalmology practice, not only in regards to eye drops but also a wide range of other products, such as surgical implants and disposable materials. In particular, the introduction of electronic information for use (e-IFU) manuals for surgical devices is important both in terms of reducing paper waste and providing surgeons with access to the most current information. Schehlein et al.⁶, highlighted the potential of using e-IFU in eye surgery to reduce packaging waste. Similarly, Stern et al.⁷ reported findings supporting digital solutions for environmental

Keywords: Ophthalmology, sustainability, recycling, digitalization

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waste reduction in the field of ophthalmology. Legal regulations in the European Union support e-IFU practices, strengthening the applicability of this approach on a global scale.⁸ The adoption of this approach in the field of ophthalmology will provide both environmental and clinical benefits.

Patients can also be encouraged to recycle empty eye drop bottles by bringing them to pharmacies. Exempting patients from paying the medication contribution (10%) as part of this process will increase recycling rates and actively involve patients in sustainable practices. The Deposit Return System (DRS), initiated in Turkey on January 1, 2025, is a similar practice that encourages the consumer to recycle beverage packaging.⁹ This proposed program for eye drop bottles will be a supportive approach that aligns with the current DRS practice. Collected bottles can be processed using appropriate recycling methods, making a tangible contribution to sustainability in the health sector.

In conclusion, eliminating eye drop boxes, providing digital package inserts, and encouraging patients to recycle empty bottles will make a valuable contribution in terms of environmental sustainability and patient-centered care. The pharmaceutical industry and regulatory authorities should consider this proposal.

Ethics

Informed Consent: Not applicable.

Declarations

Authorship Contributions

Concept: B.DK, H.B., Design: B.DK, H.B., Data Collection or Processing: B.DK, H.B., Analysis or Interpretation: B.DK, H.B., Literature Search: B.DK, H.B., Writing: B.DK, H.B.

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Anti-VEGF Treatment for Bilateral Choroidal Neovascularization Secondary to Laser Pointer Injury in a Child: Case Report

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Dear Editor,

Laser pointers are low-energy light sources that emit focal non-ionizing radiation and are commonly used in medicine, industry, and entertainment.^{1,2} In recent years, laser pointer-induced retinal injuries have increased, particularly among children.³

This article describes a 7-year-old patient with bilateral laser-maculopathy who showed rapid progression of type 2 choroidal neovascularization (CNV) in the right eye (RE) and suspected CNV in the left eye (LE) after accidental exposure to a class 3R handheld laser pointer. This case emphasizes the importance of recognizing the development of choroidal vascularization following laser pointer-induced maculopathy.

A healthy 7-year-old boy presented to our clinic with blurred vision in both eyes after playing with a laser pointer the day before. On examination, best corrected visual acuity (BCVA) was 20/40 in the RE and counting fingers at 30 cm in the LE. Anterior segment examination was unremarkable in both eyes. Fundus examination revealed two juxtafoveal yellowish-gray spots in the RE and an elevated hemorrhagic foveal lesion in the LE ([Figure 1a, b](#)). Spectral domain optical coherence tomography

(SD-OCT) revealed no pathological findings in the RE but showed a discrete hyperreflective lesion beneath the fovea and an intraretinal cyst in the LE ([Figure 1c, d](#)). OCTA displayed normal findings on all slabs in the RE and a black shadow from the blocking effect of the hemorrhage in the LE ([Figure 1e, f](#)). Fundus fluorescein angiography (FFA) showed hyperfluorescent staining of the two juxtafoveal spots in the RE and normal findings in the LE ([Figure 1g, h](#)).

Under general anesthesia, an early sub-Tenon injection of triamcinolone acetonide (40 mg/mL; Kenacort-A 40®, Bristol-Myers Squibb, Anagni, Italy) was administered in both eyes. Topical nepafenac 0.1% (Apfector®, Bilim Pharmaceuticals, İstanbul, Türkiye) and oral ibuprofen syrup (İbufen®, Sanofi Pharmaceuticals, İstanbul, Türkiye) were also prescribed. After 5 days, BCVA improved to 20/25 in the RE and 20/125 in the LE. On day 6, SD-OCT revealed a new foveal ellipsoid zone defect in the RE, along with regression of the hyperreflective lesion and a decrease in central macular thickness in the LE.

At 2-week follow-up, BCVA in the RE had decreased to 20/50 and remained unchanged in the LE. Fundus examination revealed a new elevated lesion in the foveal area besides the two juxtafoveal yellowish spots in the RE and a persistent elevated hemorrhagic foveal lesion in the LE, arousing suspicion of CNV. SD-OCT showed the presence of intraretinal and subretinal fluid in the RE, along with the persistent hyperreflective lesion in the LE ([Figure 2a, b](#)). The outer retinal slab of OCTA depicted CNV in the RE and a prominent black shadow in the LE ([Figure 2c, d](#)). FFA revealed early hyperfluorescence of the lacy network indicating type 2 CNV in the RE, while no leakage was observed in the LE ([Figure 2e, f](#)).

The patient received consecutive monthly intravitreal injections of 1 mg aflibercept (Eylea®, Bayer AG, Berlin, Germany) three times in both eyes under general anesthesia. Within one month, regression of the CNV in the RE was observed, accompanied by an improvement in BCVA up to 20/25 in both eyes. Subsequent follow-up SD-OCT revealed the presence of juxtafoveal scar tissue without exudation in the RE and almost complete regression of the hyperreflective lesion

Keywords: Laser pointer, maculopathy, choroidal neovascularization, anti-VEGF, pediatric retinal injury, SD-OCT, OCTA, sub-tenon steroid injection, retinal imaging

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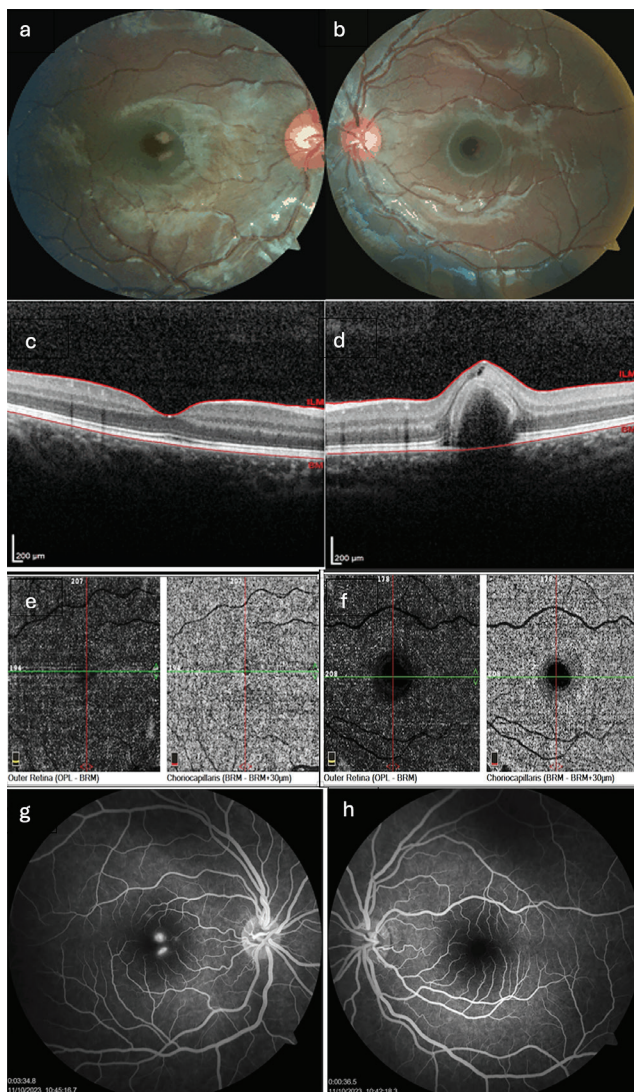


Figure 1. Dilated fundus examination revealed two juxtafoveal yellowish-gray spots in the right eye (RE) (a) and an elevated hemorrhagic foveal lesion in the left eye (LE) (b). While SD-OCT demonstrated no pathological findings in the RE (c), it revealed a discrete hyperreflective lesion beneath the fovea, disruption of the outer retina, loss of the ellipsoid zone, and an intraretinal cyst in the LE (d). OCTA depicted normal findings on all slabs in the RE (e) and a black shadow from the blocking effect of the hemorrhage on the outer retinal and choriocapillaris slabs in the LE (f). FFA showed hyperfluorescent staining of the two juxtafoveal spots in the RE (g) and normal findings in the LE (h).

SD-OCT: Spectral domain optical coherence tomography, OCTA: OCT angiography, FFA: Fundus fluorescein angiography

suspected to be CNV in the LE (Figure 3a, b). OCTA depicted a change from a dense to a loose configuration of CNV on outer retinal slabs in the RE, while normal findings were observed on all slabs in the LE. Fundus examination revealed regression of the elevated foveal lesion in both eyes after the monthly intravitreal injections (Figure 3c, d).

Laser devices are classified based on their power output, with class III and IV lasers (>1 mW) posing significant risks to the

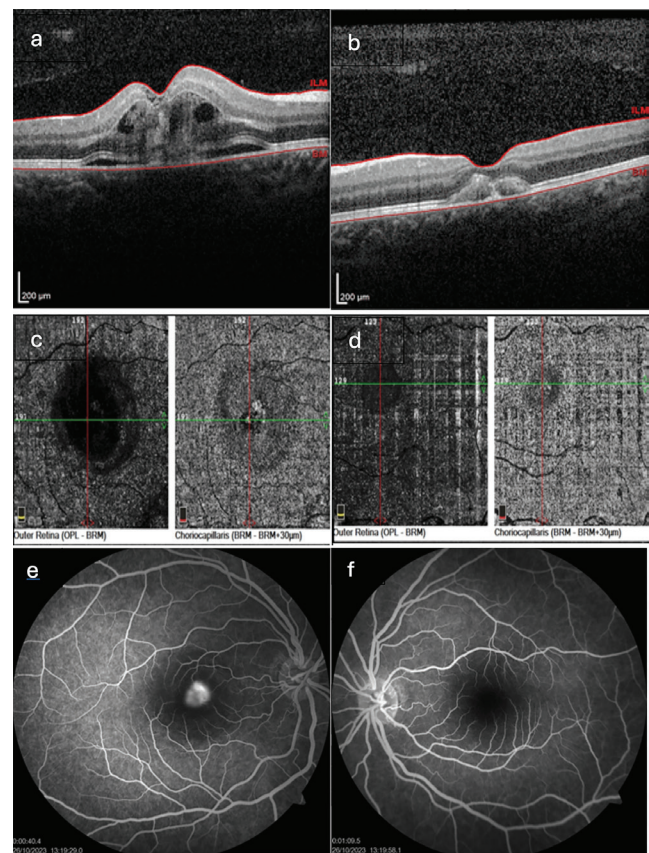


Figure 2. SD-OCT revealed intraretinal and subretinal fluid in the right eye (RE) (a), persistent hyperreflective lesion in the left eye (LE) (b). The outer retinal slab of OCTA depicted CNV with a dark halo in the RE (c) and a prominent black shadow in the LE (d). FFA unveiled early hyperfluorescence of the lacy network indicating type 2 CNV formation in the RE (e), while normal findings were observed in the LE (f).

SD-OCT: Spectral domain optical coherence tomography, OCTA: OCT angiography, CNV: Choroidal neovascularization, FFA: Fundus fluorescein angiography

retina.⁴ In recent years, laser pointer–associated retinal injuries have increased due to misclassified devices often marketed as toys.⁵ Children and other vulnerable groups are at particularly high risk of irreversible ocular damage.⁴ This case highlights the potential for bilateral retinal injury from class 3R pointers and the value of multimodal imaging. Swept-source OCT studies, such as that conducted by Moussa et al.,⁶ further expanded the understanding of the clinical spectrum of laser pointer maculopathy.

Currently, no consensus exists regarding treatment of laser-induced retinal injuries. Some reports describe improved OCT findings and BCVA after systemic steroid use, while experimental studies suggest non-steroidal anti-inflammatory drugs (NSAIDs) may enhance photoreceptor survival following argon laser injury.^{7,8} However, randomized trials have not demonstrated clear benefits for either treatment. Early sub-Tenon steroid injection has been proposed as a means of achieving rapid visual recovery while minimizing systemic effects.⁹ In our patient,

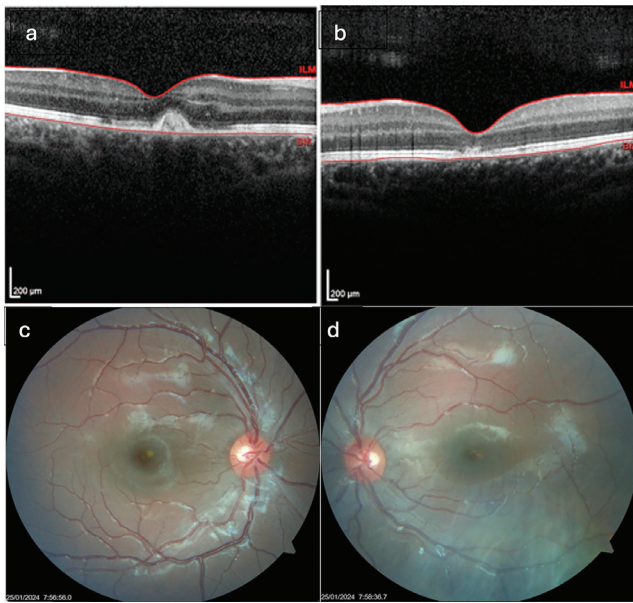


Figure 3. SD-OCT showed juxtafoveal scar tissue without exudation after three anti-VEGF injections in the right eye (a) and almost complete regression of the hyperreflective lesion with recovery of the outer retina after two anti-VEGF injections in the left eye (b). Dilated fundus examination revealed regression of the elevated foveal lesion in both eyes (c, d)

SD-OCT: Spectral domain optical coherence tomography, VEGF: Vascular endothelial growth factor

this approach combined with topical and oral NSAIDs led to temporary structural and functional improvement. Nonetheless, CNV developed in the RE within two weeks, and complete regression of the retinal injury in the LE could not be achieved with steroids alone.

Anti-vascular endothelial growth factor (anti-VEGF) therapy has emerged as the most effective strategy for CNV secondary to laser pointer injury.² Case reports have shown either complete CNV resolution or significant visual recovery in young patients, sometimes after only a single injection.¹⁰ Consistent with this, our patient received three monthly intravitreal injections in the RE, resulting in full CNV inactivation and rapid functional recovery, with no recurrence during follow-up. In the LE, where hemorrhage obscured imaging but CNV was suspected, anti-VEGF therapy under general anesthesia also achieved favorable outcomes.

In summary, while steroids and NSAIDs may provide early structural improvement, they appear insufficient to prevent CNV. Anti-VEGF therapy remains the cornerstone in managing neovascular complications of laser pointer injuries. Given the rising incidence of such injuries, especially among children, stricter regulation of handheld lasers and public education

are urgently needed. Early recognition and timely anti-VEGF treatment offer the best chance for preserving long-term vision.

Ethics

Informed Consent: Written consent was obtained from the parent of the patient.

Declarations

Authorship Contributions

Surgical and Medical Practices: S.A.B., G.G., Concept: S.A.B., S.E.G., Design: G.Y., S.A.B., S.E.G., Data Collection or Processing: S.E.G., G.G., Analysis or Interpretation: G.Y., S.E.G., Literature Search: S.E.G., Writing: S.E.G.

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Letter to the Editor Re: “Comparison of 20% Autologous Platelet-Rich Plasma Versus Conventional Treatment in Moderate to Severe Dry Eye Patients”

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Dear Editor,

We read with great interest the study by Sachan et al.¹ examining the comparative efficacy of autologous platelet-rich plasma (aPRP) and conventional therapy for moderate-to-severe dry eye disease. The authors should be commended for implementing a robust design with clearly defined outcome measures and a meaningful follow-up period. While the therapeutic benefits of aPRP are compelling, we identified methodological and interpretive issues that affect the strength of clinical inferences, particularly regarding the evaluation of treatment response. Chief among these is the reliance on mean group differences in Ocular Surface Disease Index (OSDI) without reporting the proportion of patients achieving a minimal clinically important difference (MCID). Statistically significant differences in OSDI scores may not equate to symptom relief that is meaningful to patients. For instance, a 15-point OSDI reduction is commonly considered the MCID

threshold.² Reporting this would have contextualized the patient-perceived benefit and helped guide clinical adoption.

Similarly, while p values are frequently cited for intergroup comparisons of secondary outcomes such as tear break-up time, Schirmer's test, and corneal fluorescein staining, these are time-varying, observer-dependent variables that can be influenced by environmental conditions.³ However, no stratified variance analysis or adjustment for within-subject correlation appears to have been performed, despite repeated measurements on the same eyes. In studies of bilateral ocular disease, paired-eye statistical models better account for intra-patient correlation than independent-sample t-tests,⁴ which were used in this study. The use of inappropriate models increases the risk of type I error, particularly with small sample sizes.

Additionally, the authors did not quantify the platelet concentration in the prepared aPRP drops. Given the direct link between platelet-derived growth factor content and epithelial recovery,⁵ the absence of dosage validation introduces uncertainty in replicability. This is clinically relevant because interindividual variability in baseline platelet levels can lead to inconsistent therapeutic effects, especially when generalizing across diverse patient populations.

Notably, the study concluded that aPRP improves visual acuity; however, the data revealed that best-corrected visual acuity (BCVA) changes were not statistically significant at any time point. Including BCVA as a primary outcome when it remained unchanged across groups risks overinterpretation, particularly when no prespecified thresholds were provided to define clinically meaningful change.

Finally, although conjunctival impression cytology data were a novel and welcome addition, the grading system used was not standardized or referenced, limiting the generalizability of the histopathologic interpretation. Without a validated scoring metric, reported cytological improvements should be interpreted with caution.

Keywords: Autologous platelet-rich plasma, dry eye disease, ocular surface health, minimal clinically important difference, statistical modeling, regenerative therapies

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Despite these concerns, this study adds value to the ongoing exploration of biologics in ocular surface disease and reflects a growing interest in patient-specific regenerative therapies. Constructive scrutiny of methodology, particularly outcome reporting and statistical modeling, is essential for translating findings into clinical practice. We appreciate the authors' contributions to this evolving field.

Declarations

Authorship Contributions

Concept: R.M., P.S., R.S., Design: R.M., P.S., R.S., Data Collection or Processing: R.M., P.S., R.S., Analysis or Interpretation: R.M., P.S., R.S., Literature Search: R.M., P.S., R.S., Writing: R.M., P.S., R.S.

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Reply

We would like to thank you for the opportunity to respond to the issues raised in the letter and to clarify aspects of our study¹ related to these concerns. We would also like to thank the authors for their interest in our paper and for taking the time to express their observations.

We totally agree that reporting the proportion of patients achieving a minimal clinically important difference (MCID) would have been better than reporting Ocular Surface Disease Index (OSDI) scores. The problem with MCID is that there is no single universally agreed upon MCID for OSDI. I would like to point out that the study provided as a reference is a neurology article.² There is no consensus on the method used to measure MCID. Also, a multitude of factors affect MCID, such as disease severity, study methodology, patient population, and treatment context. A key study published in 2010 established the following MCID ranges for OSDI: improvement of 4.5 to

7.3 points for mild to moderate disease and 7.3 to 13 points for severe disease.³ However, we completely agree that once a single universally agreed upon OSDI MCID value is obtained, including it for calculation of symptom improvement will be of paramount importance.

We acknowledge the authors' concern regarding the potential for type I error due to repeated measures and intra-patient correlation in bilateral ocular disease. While regression models are more suitable for prediction analyses, in our study we primarily compared mean values between two groups. To address their concern, we re-analyzed the data with Bonferroni correction applied to control for type I error. The mean, standard deviation, and p-values remain unchanged. We appreciate this suggestion, as it has helped strengthen the statistical rigor of our results.

In this study, outcomes from both eyes were used. The results from this analysis are usually unbiased and the variance of estimate is similar to using all of the data with appropriate accommodation of correlation.⁴ Regarding the use of a paired-eye statistical model and stratified variance analysis, we will try to incorporate these suggestions in our future studies. Also, we totally agree that platelet concentration should have been quantified in the prepared aPRP drops, especially the stored ones. We are very thankful for the suggestion and will definitely implement this approach going forward.

Regarding best corrected visual acuity (BCVA), I would like to clarify that the phrase "improved visual acuity" appears only once in the article, in a sentence citing references 17 and 18.^{5,6} Therefore, it was an observation of other researchers. We clearly stated that the improvement in BCVA in the study group, while potentially relevant, did not reach statistical significance.

The grading system of impression cytology has been referenced as early as 1984⁷ and as recently as 2025.⁸ Therefore, it is a well standardized and referenced grading system. However, I agree that a scoring metric would have been better for objective quantification.

In summary, we are thankful to receive so much interest in our article. We truly acknowledge the appreciation of our study and will try to incorporate the suggestions in our future research.

Declarations

Authorship Contributions

Analysis or Interpretation: S.S., S.P.S., S.K., V.K.S., K.D., Literature Search: S.S., K.D., Writing: S.S., K.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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