Effects and Prognosis of Cataract Surgery in Patients with Retinitis Pigmentosa

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ABSTRACT

Introduction: Cataract extraction could improve visual acuity (VA) for patients with retinitis pigmentosa (RP), while the surgery may increase photoreceptor degeneration through light damage. In this study, we conducted a systematic review and meta-analysis to investigate the effectiveness and prediction of VA after cataract surgery in patients with RP.

Methods: We comprehensively extracted data from literature of available studies with quality control processing. Improvement of VA before and after cataract surgery of different durations of follow-up and different structural integrity of the preoperative macular ellipsoid zone (EZ) in patients with RP were compared. VA was measured by the logarithm of the minimum angle of resolution (logMAR).

Results: Sixteen studies were subjected to analysis. Postoperative VA was significantly improved versus preoperative, with a mean difference (MD) of 0.57 [95% confidence interval (CI) 0.45, 0.69], and a fixed-effect model was applied during follow-up durations of 1 day to 1 month ($I^2 = 0\%$). Similarly, for follow-up durations of 1–3 months, 3–6 months, and 6–12 months, postoperative VAs were all better than preoperative values, with MDs of 0.36 (95% CI 0.31, 0.41), 0.35 (95% CI 0.23, 0.46), and 0.22 (95% CI 0.14, 0.30) ($I^2 < 50\%$). For follow-up duration of 1–5 years, the random-effect model was applied for higher heterogeneity ($I^2 = 81\%$), with an MD of 0.26 (95% CI 0.09, 0.43). There was no significant difference in the improvement of the EZ-invisible group, with an MD of 0.27 (95% CI 0.17, 0.70) ($I^2 = 82\%$). There were significant differences between EZ-abnormal and EZ-normal groups in preoperative and postoperative VA, with MDs of 0.56 (95% CI 0.27, 0.85) and 0.46 (95% CI 0.27, 0.65) ($I^2 > 50\%$).

Conclusions: Cataract surgery could improve VA for patients with RP during long-term follow-up, and the surgery is not recommended for patients with invisible preoperative macular EZ. However, further studies are required to address the problem of excessive light exposure to the degenerated retina in patients with RP with the cataract removed. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022340165).
**INTRODUCTION**

Retinitis pigmentosa (RP), the most common genetic ocular disease, is one of the leading causes of vision loss across the world [1]. The prevalence of RP varies from 1:13,121 in Spain [2], 1:9000 in Korea for all ages [3], 1:4000 in China for those over 55 years of age [4] to 1:750 in the adult population of rural Central India [5]. RP is characterized by progressive dysfunction of rod photoreceptors, followed by degeneration of cone photoreceptors. The inheritance patterns of RP are autosomal recessive, autosomal dominant, and X-linked. As for sporadic RP cases, causal autosomal dominant and X-linked variants were found in over 7.5% of cases [6].

The typical abnormalities in the fundus were bone spicule pigmentation, attenuation of retinal vessels, and waxy pallor of the optic nerve head, which result in the symptom of night blindness in the initial to central vision loss [1] (Fig. 1).

Besides the continuous progressive degeneration of photoreceptors and retinal pigment epithelium, complications such as cataracts and cystoid macular edema (CME) also could damage the remaining sight. It was reported that CME and cataracts were present in 58.6% and 23.4% of patients with RP, respectively [7]. Visual acuity (VA) could be improved for the complications that receive effective treatment, especially with the improvement of the cataract surgery pattern, which has been regarded as an efficient and safe surgery. Cataract surgery could improve the VA in patients with RP; however, it is still controversial whether or not performing surgery is necessary for patients with RP, as cataract extraction may increase photoreceptor degeneration through light damage [8], which could accelerate the deterioration of the patient’s VA and increase complications such as posterior capsule opacification postoperatively.

The aim of this study is to evaluate the changes in VA before and after cataract surgery in patients with RP and whether the preoperative ellipsoid zone (EZ) examined by optical coherence tomography (OCT) could predict the final VA after cataract surgery in patients with RP. In this context, we investigate the improvements of VA during different durations of follow-up and different preoperative EZ conditions.

**METHODS**

**Study Protocol**

The systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [9]. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022340165), on 27 June 2022.
Inclusion Criteria

Retrospective, observational studies, case series, cross-sectional, cohort, case-control studies, and randomized controlled trials could all be included. The target population was patients with RP who underwent cataract surgery (phacoemulsification and intraocular lens implantation or extracapsular cataract extraction for those complicated cases).

Exclusion Criteria

The exclusion criteria were (1) non-English or Chinese articles; (2) studies without full-text articles or studies that do not contain primary data in their published articles, and we were unsuccessful in obtaining the original data from the authors; (3) animal and experimental studies; and (4) unpublished records such as conference papers, theses, and patents; (5) patients with uveitis or any disease that could cause RP-like fundus improvements or combined other ocular diseases, like glaucoma and complete luxation of the lens.

Databases and Search Strategy

A literature search was implemented in public databases, PubMed, Web of Science, Medline, the Chinese National Knowledge Infrastructure (CNKI), the Wanfang database, and the VIP database, from January 1, 2000 to May 31, 2022, using key and MeSH terms: retinitis pigmentosa; RP; cataract. The search strategy was ((retinitis pigmentosa) OR (RP)) AND (cataract), (“retinitis pigmentosa” [MeSH Terms] OR (“retinitis” [All Fields] AND “pigmentosa” [All Fields]) OR “retinitis pigmentosa” [All Fields] OR “RP” [All Fields]) AND (“cataract” [MeSH Terms] OR “cataract” [All Fields] OR “cataracts” [All Fields] OR “cataractic” [All Fields] OR “cataractous” [All Fields]).

Outcomes and Outcome Measurement

Improvement of VA During Different Durations of Follow-Up

We compared preoperative and postoperative VA in patients with RP and cataract according to different durations of follow-up after cataract surgery: (1) 0 months < postoperative ≤ 1 month; (2) 1 month < postoperative ≤ 3 months; (3) 3 months < postoperative ≤ 6 months; (4) 6 months < postoperative ≤ 12 months; and (5) 12 months < postoperative ≤ 60 months.

Changes of VA in Preoperative and Postoperative of Each EZ Grade

According to the OCT images, the preoperative conditions of the EZ were graded into the EZ-invisible group (invisible EZ in the macular
region), the EZ-abnormal group (visible but discontinuous EZ in the macular region), and the EZ-normal group (complete EZ in the macular region).

**Postoperative Complication**
We reviewed posterior capsular opacification, CME, and other rare postoperative complications.

For the measurement of VA, 13 studies used the logarithm of the minimum angle of resolution (logMAR) for a statistical presentation and three studies used decimal acuities for statistical evaluation, which were converted into logMAR by the formula of logMAR = \(-\log (\text{decimal acuity})\) [10].

**Data Extraction**

**Study Selection**
Two authors (HLH, XDM) searched and screened the titles and abstracts independently for all articles from the aforementioned databases on the basis of a predefined selection protocol. Decisions were recorded using the PRISMA flowchart.

**Data Extraction**
Data extraction was done independently by two team members; reappraisal and checking of disagreements was done by them together (HLH, XDM). If disagreements were not resolved, a third reviewer (HS) was consulted. The following data were extracted: (1) author and year of the study; (2) design of the study; (3) the number of participants and eyes included in the study; and (4) main (VA) and additional (CME and posterior capsular opacification) outcome measures with their follow-up time.

**Assessment of Risk of Bias and Paper Quality**
The quality of the studies was assessed by two researchers (HLH, XDM) using the modified Newcastle–Ottawa scale (NOS) reported by Modesti and colleagues [11], which considers the selection (maximum 5 stars): (1) representativeness of the sample; (2) sample size; (3) non-respondents; (4) ascertainment of the exposure (risk factor); comparability (maximum 2 stars); outcome (maximum 3 stars): (1) assessment of the outcome; (2) statistical test. A study with a score higher than 6 could be included for meta-analysis; a study scoring more than 7 is considered as being of high quality. Consensus was achieved through discussion with the third reviewer (HS) in the event of any disagreements between the researchers regarding individual ratings. Publication bias was assessed and checked by Egger’s test [12].

**Data Synthesis and Statistical Analysis**
We used a fixed-effects model or a random-effects model to calculate the mean difference (MD) and 95% confidence interval (95% CI). Heterogeneity was checked using the Q test and I² test. A P value for the Q test of less than 0.05 and/or I² greater than 50% suggested high heterogeneity, in which case a random-effects model was used; otherwise, the fixed-effects model was used. All analyses will be performed using RevMan 5.3 and GraphPad Prism 9. Egger’s test was further tested for publication bias by the R program (version 3.4). P value less than 0.05 is considered statistically significant.

**Ethics**
This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The patient whose eyes are shown in Fig. 1 provided signed informed consent.

**RESULTS**
More than 4500 records were identified through database searching (Fig. 2). We included 19 articles assessed for eligibility, there were 5 Chinese studies and 14 English studies. One Chinese article [13] was excluded because of insufficient data (no duration of follow-up) and two English articles were excluded because the
Results had been repeatedly reported by the same research group [14, 15]. The remaining 16 studies [16–31] were included for data analysis. The flowchart of the selection process is shown in Fig. 2. All studies were retrospective and observational studies. VA in three studies was converted from decimal acuity into logMAR by the formula in “Postoperative Complication”. In the meta-analysis, a total of 796 patients (1133 eyes) were included. Characteristics of include 16 studies are shown in Table 1. The follow-up time ranged from 1 day to 60 months.

Risk of Bias Assessment

As shown in Table 2, the average number of stars of included studies scored by modified NOS was 8.5, and all included studies were of
Table 1 Characteristics of included studies

| Author                | Year | Design                      | No. of patients | No. of eyes | Duration of follow-up (months) |
|-----------------------|------|-----------------------------|-----------------|-------------|-------------------------------|
| Jackson [16]          | 2001 | Retrospective analysis      | 89              | 142         |                               |
| Dikopf [17]           | 2013 | Retrospective observational case series | 47              | 80          | ✓                             |
| Bayyoud [18]          | 2013 | Retrospective study         | 52              | 46          | ✓                             |
| Garcia-Martín [19]    | 2013 | Observational cross-sectional study | 35              | 35          | ✓                             |
| Nakamura [20]         | 2014 | Retrospective case study    | 43              | 58          | ✓                             |
| Chan [21]             | 2017 | Retrospective study         | 42              | 67          | ✓                             |
| De Rojas [22]         | 2017 | Retrospective cohort study  | 19              | 19          | ✓                             |
| Lu [23]               | 2017 | Retrospective study         | 52              | 101         | ✓                             |
| Mao [24]              | 2018 | Retrospective, observational study | 70              | 109         | ✓                             |
| Fan [25]              | 2019 | Retrospective study         | 16              | 24          | ✓                             |
| Wang [26]             | 2020 | Retrospective case series study | 7               | 14          | ✓                             |
| Zhang [27]            | 2020 | Retrospective study         | 38              | 58          | ✓                             |
| Chatterjee [28]       | 2021 | Retrospective case series study | 103             | 132         | ✓                             |
| Chen [29]             | 2021 | Retrospective cases series study | 63              | 84          | ✓                             |
| Miura [30]            | 2021 | Retrospective, observational case series | 62              | 62          | ✓                             |
| Nakamura [31]         | 2021 | Retrospective, observational study | 64              | 96          | ✓                             |

high quality with modified NOS ≥ 7 stars. VA and complications of the included 16 studies were self-reported and not obtained by independent blind assessment or record linkage with an assessment of outcome and therefore scored only 1 star. The sample size of studies by De Rojas et al. and Wang et al. was less than 20 eyes, and therefore scored no stars. VA in three studies was recorded by decimal acuity which needs to be converted into logMAR; thus, 1 star was deducted from the ascertainment of exposure score. Chatterjee and colleagues’ study scored 1 star in comparability for the different surgery methods with phacoemulsification, manual small incision cataract surgery, and extracapsular cataract extraction, and Nakamura’s study scored 1 star for including patients from previous studies.

The results of Egger’s test shown in Table 3 indicate that there is no publication bias for the included studies.
Table 2 Modified NOS for risk of bias assessment

| Author          | Selection | Comparability | Outcome | Score |
|-----------------|-----------|---------------|---------|-------|
|                 | Representativeness of sample | Sample size | Non-respondents | Ascertainment of exposure | Assessment of outcome | Statistical test |       |
| Jackson [16]    | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Dikopf [17]     | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Bayyoud [18]    | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Garcia-Martin [19] | 1       | 1             | 1       | 2     | 2     | 1     | 1     | 8     |
| Nakamura [20]   | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Chan [21]       | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| De Rojas [22]   | 1         | 0             | 1       | 2     | 2     | 1     | 1     | 8     |
| Lu [23]         | 1         | 1             | 1       | 1     | 2     | 1     | 1     | 8     |
| Mao [24]        | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Fan [25]        | 1         | 1             | 1       | 2     | 2     | 1     | 0     | 8     |
| Wang [26]       | 1         | 0             | 1       | 1     | 2     | 1     | 1     | 7     |
| Zhang [27]      | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Chatterjee [28] | 1         | 1             | 1       | 2     | 1     | 1     | 1     | 8     |
| Chen [29]       | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Miura [30]      | 1         | 1             | 1       | 2     | 2     | 1     | 1     | 9     |
| Nakamura [31]   | 1         | 1             | 1       | 2     | 1     | 1     | 1     | 8     |
Improvement of VA During Different Durations of Follow-Up

We found that VA during postoperative follow-up duration of 1 day to 1 month was better than preoperative VA, with an MD of 0.57 (95% CI 0.45, 0.69), with no heterogeneity among studies ($I^2 = 0\%$ and $P < 0.05$); hence, we applied a fixed-effects model. Similarly, for follow-up durations of 1 month to 3 months, 3 months to 6 months, and 6 months to 1 year, postoperative VAs were all better than preoperative VAs, with MDs of 0.36 (95% CI 0.31, 0.41), 0.35 (95% CI 0.23, 0.46), and 0.22 (95% CI 0.14, 0.30), with quite small heterogeneity ($I^2 = 0\%$, 0%, and 37%), and there was no publication bias for all aforementioned outcomes by Egger’s test. As for follow-up duration of 1–5 years, we applied the random-effect model for higher heterogeneity for a larger span of follow-up, with $I^2 = 81\%$, MD was 0.26 (95% CI 0.09, 0.43) (Figs. 3, 4, 5, 6, 7).

We found with the extended follow-up, improvement of VA between preoperative and postoperative periods showed a downward trend until the follow-up duration of 12 months. Surprisingly, the downward trend was reversed with follow-ups of more than 1 year (Fig. 8).

Changes of Preoperative and Postoperative VA of Each EZ Grade

There was no significant difference in the improvement of the EZ-invisible group ($P = 0.23$), with an MD of 0.27 (95% CI −0.17, 0.70), with an $I^2 = 82\%$, a random-effects model was applied. Changes in preoperative and postoperative VA in EZ-abnormal and EZ-normal groups were significant, with MDs of 0.56 (95% CI 0.27, 0.85) and 0.46 (95% CI 0.27, 0.65), a random-effects model was applied for $I^2 > 50\%$ (66% and 69%) (Figs. 9, 10, 11, 12). The result of Egger’s test showed that there is no publication bias for the included studies ($P > 0.05$).

Postoperative Complications

As shown in Table 4, among the 16 included articles, 11 reported complications after surgery in patients with RP and cataract. Posterior capsule opacification was the most common complication, with a prevalence of 42.63% (347/814). CME was observed in three studies (28 eyes). Postoperative complications include zonular dialysis in 20 eyes, capsule contraction syndrome in 12 eyes, and an increase in intraocular pressure noted in 5 eyes. Other rare complications were reported by Chatterjee and colleagues (two eyes suffered posterior capsule rupture, 33 eyes foveal thinning, 58 eyes optic atrophy, and 5 eyes postoperative uveitis) and by Nakamura and colleagues (two eyes suffered epiretinal membrane, one eye macular hole, and one eye vitreomacular traction syndrome).

DISCUSSION

Cataract extraction for patients with RP combined with cataracts could help most patients enhance VA and improve their quality of life. As a result of the progressive degeneration of photoreceptors, postoperative complications, inflammatory response following surgery, and retinal damage during light exposure, where photopigment, retinoids, and bisretinoids may play important roles in photochemical damage,
conclusions from studies on the long-term effects after cataract surgery in patients with RP gave contradictory answers [22, 32]. Moreover, not all patients are suitable for cataract surgery because it is difficult to improve VA as a result of deteriorated preoperative retinal conditions.

Hence, we conducted this systematic review and meta-analysis to investigate the improvements of VA during different durations of follow-up and different preoperative EZ conditions to predict postoperative VA.

Fig. 3 Forest plot of improvement of VA during follow-up durations of (0,1] month

Fig. 4 Forest plot of improvement of VA during follow-up durations of (1,3] months

Fig. 5 Forest plot of improvement of VA during follow-up durations of (3,6] months

Fig. 6 Forest plot of improvement of VA during follow-up durations of (6,12] months
In the present systemic meta-analysis, the evidence is clear that cataract surgery could help improve VA after cataract surgery in patients with RP during all durations of follow-up. Our meta-analysis showed that postoperative VA could be up 0.22 to 0.57 log units higher than preoperative VA. And we found that the improvement of VA showed a downward trend with the extended follow-up of 1 day to 12 months. This indicated that postoperative VA would decrease with the passage of time, and there are several factors mentioned above.
that contribute to this result. However, the postoperative VA is still better than preoperative VA. Surprisingly, the downward trend in VA reversed with a follow-up of more than 1 year; one contribution to this observation may be that the postoperative complication of posterior capsule opacification usually occurs 6 months to 1 year after surgery, for which patients prefer to seek treatment by neodymium:yttrium–aluminum–garnet (Nd:YAG) laser capsulotomy to regain part of their vision [33].

In this meta-analysis, we also evaluated the VA outcomes after cataract surgery in patients with RP with different structural integrity of the preoperative macular EZ examined by OCT. We found no difference between preoperative and postoperative VA in the EZ-invisible group. As for the EZ-abnormal group and EZ-normal group, the difference between preoperative and postoperative VA was statistically significant and up to 0.56 and 0.46 log units for those patients with RP. Greater improvement of VA in the EZ-abnormal group than the EZ-normal group may in part be due to the baseline VA in the EZ-abnormal group being worse and combined with more severe cataracts. Hence, we do not recommend cataract surgery for patients with EZ-invisible RP, who will not improve their VA after the surgery and OCT should be examined for patients with RP before cataract surgery.

We also reviewed the postoperative complications which could affect VA after cataract surgery. Posterior capsule opacification and CME were the most common complications. Strong et al. [34] concluded that the mechanisms for RP-associated CME include breakdown of the blood—retinal barrier, dysfunction of retinal pigment epithelial in pumping, vitreous traction, and edema of Müller cells and antiretinal antibodies. CME remains one of the most frequent complications of cataract surgery whose procedure could increase the risks for patients with RP [35]. And CME has been found to cause the formation of macular holes, and surgery of vitrectomy could significantly improve VA [36]. Zonular dialysis or dislocation of intraocular lens, posterior capsule rupture, postoperative uveitis, and epiretinal membrane were also reported. Some studies focused on capsule contraction syndrome, especially investigating the effect of with or without lens capsular tension ring on patients with RP. And capsular tension ring could reduce the complications caused by capsule contraction as usual in patients with cataracts. Dikopf and colleagues [17] found that 18.8% of eyes had some degree of zonular insufficiency and 10% of eyes had phacodonesis during surgery in patients

Fig. 11 Forest plot of changes of preoperative and postoperative VA in the EZ-normal group

Fig. 12 Summary results of changes of VA in each EZ grade

| EZ Grade    | No. of patients | No. of trials | Changes of BCVA (logMAR) | Mean difference [95% CI] | Heterogeneity |
|-------------|----------------|---------------|--------------------------|--------------------------|---------------|
| EZ-invisible | 67             | 4             | 0.27 [-0.17, 0.70]       |                           | η²=82%        |
| EZ-abnormal  | 66             | 4             | 0.56 [0.27, 0.85]        |                           | η²=66%        |
| EZ-normal    | 103            | 4             | 0.46 [0.27, 0.65]        |                           | η²=69%        |
with RP, which was higher than the 0.1% of senile cataract eyes that had developed zonular dialysis intraoperatively [37]. Hence, for patients with RP, the capsular tension ring, suitable size, and haptic geometry intraocular lens are highly recommended [38], while

| ID          | No. of eyes | PCO | CME | CCS | Zonular dialysis/IOL dislocated | IOP elevated | Others                                         |
|-------------|-------------|-----|-----|-----|---------------------------------|--------------|-----------------------------------------------|
| Jackson 2001 [16] | 142         | 118 | 20  | –   | –                               | –            | –                                             |
| Dikopf 2013 [17]   | 80          | 66  | –   | –   | 18                              | –            | –                                             |
| Bayyoud 2013 [18]   | 52          | 23  | 2   | 2   | –                               | –            | –                                             |
| De Rojas 2017 [22]  | 19          | 18  | –   | –   | –                               | –            | –                                             |
| Mao 2018 [24]       | 109         | –   | –   | –   | 2                               | –            | –                                             |
| Fan 2019 [25]       | 24          | 5   | –   | –   | –                               | 3            | 4 eyes corneal edema                          |
| Wang 2020 [26]      | 14          | –   | –   | 1   | –                               | –            | –                                             |
| Chatterjee 2021 [28]| 132         | 22  | 6   | –   | 2                               | –            | 2 eyes posterior capsule rupture; 33 eyes foveal thinning; 58 eyes optic atrophy; 5 eyes postoperative uveitis |
| Chen 2021 [29]      | 84          | –   | 4   | –   | –                               | –            | –                                             |
| Miura 2021 [30]     | 62          | 44  | –   | –   | –                               | –            | –                                             |
| Nakamura 2021 [31]  | 96          | 51  | –   | 3   | –                               | –            | 2 eyes epiretinal membrane; 1 eye macular hole; 1 eye vitreomacular traction syndrome |

*PCO* posterior capsule opacification, *CME* cystoid macular edema, *CCS* capsular contraction syndrome, *IOL* intraocular lens, *IOP* intraocular pressure
aggressive polishing of the capsule is suboptimal for preventing PCO in patients with zonular weakness RP [17]. However, further studies are required to address the problem of excessive light exposure to the degenerated retina in patients with RP with the cataract removed. As for late-stage patients with RP, the replacement of dead cells with diverse retinal cell types derived from pluripotent stem cells, including RPE cells and photoreceptors, may be a strategy to rescue the visual function of retinal degeneration [39, 40]. Moreover, the identification of novel genotype–phenotype correlations and the mutation spectrum should also be studied to assist in both the clinical diagnosis and the development of treatments for inherited retinal dystrophy, like RP. Our team has discovered AHI1 as a novel candidate gene for nonsyndromic RP by developing a targeted panel, which was previously reported to cause a congenital systemic disease called Joubert syndrome [41].

In conclusion, cataract surgery could improve VA for patients with RP and cataract during the long-term follow-up, although changes in VA showed a downward trend. Moreover, cataract surgery is not recommended for patients with EZ-invisible RP, and OCT should be examined for patients with RP before cataract surgery.

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Author Contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Hailong He, Hao Song, Xiaodie Meng, Kai Cao, and Yi-Xin Liu. The first draft of the manuscript was written by Hailong He, Zi-Bing Jin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The patient whose eyes are shown in Fig. 1 provided signed informed consent.

Data Availability. The datasets generated during and analyzed during the current study are not publicly available due to the need for further research but are available from the corresponding author on reasonable request.

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