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Abstract

Purpose: To identify the risk factors for a recurrence of a bleb-related infection (BRI).

Study Design: Retrospective cohort study.

Methods: The medical records of all patients diagnosed with BRI at Gifu University Hospital between January 1989 to December 2020 were reviewed. The time when the conjunctival hyperemia could not be detected and when the anterior chamber was quiet were defined as the resolution time of the BRI. The primary endpoint was a recurrence of a BRI. Kaplan-Meier estimation and the Cox proportional hazards model were used to determine the risk of a recurrence from the initial onset data of each eye. Bacteriological studies were performed to determine the pathogen causing the BRI.

Results: There were 108 eyes of 103 patients who were followed for at least 3 months after the initial BRI. A recurrent bleb infection developed in 21 (19.4%) eyes of 21 patients (13 men, 8 women). Log-rank test at the 10-year follow-up examination revealed that hypotony at the onset of the BRI (P=0.004), the prophylactic use of topical antibiotics at the onset of the BRI (P=0.046), and bleb leakage after the resolution of the BRI (P=0.021) were significantly associated with a recurrence of the BRI. The Cox proportional hazards model showed that ocular

hypotony at the onset of the BRI (unadjusted, *P*=0.007; adjusted for bleb leakage, *P*=0.015) and bleb leakage after the resolution of the BRI (unadjusted, *P*=0.027; adjusted for hypotony, *P*=0.024) were significantly associated with the recurrence of a BRI. The other factors were not significantly association with the recurrence of a BRI.

Conclusion: We recommend close observations when a bleb leakage is detected after the BRI has resolved.

Key words: bleb-related infection, recurrence of bleb-related infection, antifibrotic agents, hypotony, bleb leakage, prophylactic use of topical antibiotics

Introduction

Trabeculectomy using antimetabolites is the most commonly performed surgery in the world for glaucoma patients who have progressive optic nerve head damage and severe visual field loss despite maximum medical therapy. [1] The antimetabolites have positive effects on the maintenance of the morphology of the blebs, but they have led to thin-walled avascular conjunctival blebs which increased the frequency of bleb-related infections (BRI). [2,3] The visual prognosis of eyes after endophthalmitis is poor [4-6] and even more so in eyes with recurrences.[7] Therefore, it is important to determine the risk factors for recurrences of BRIs. At present, there are only two reports that statistically analyzed the risk factors for a recurrence of BRIs. [8,9]

Thus, the purpose of this study was to determine the risk factors for a recurrence of BRIs. To accomplish this, we reviewed the medical records of patients treated at the Gifu University Hospital who had undergone trabeculectomy.

Materials and methods

The protocol for this retrospective cohort study was approved by the Institutional Review Board of The Gifu University Hospital (decision number: 29-336, approval date: November 30, 2020). We reviewed the medical records of all patients

diagnosed with BRI in the database of the Gifu University Hospital between January 1989 to December 2020.

Patients receiving 5-fluorouracil (5-FU) were given 5 mg of 5-FU once a day throughout the first postoperative week, then once every other day for the second postoperative week. Thus, each patient received 50 mg of 5-FU in 2 weeks. Patients receiving mitomycin C (MMC) were given from 0.02 to 0.2 mg in 0.04% MMC. The MMC was dissolved in 0.5 ml of distilled water and absorbed by sponges (Spongel, Yamanouchi Pharmaceuticals, Tokyo, Japan). The sponge was applied to the exposed tissues including the posterior surfaces of the conjunctiva and Tenon's capsule, scleral flap, and adjacent episcleral tissue for 5 minutes. After 5 minutes, the wound was irrigated with 250 ml of a balanced salt solution.

Late-onset cases in which the infections developed 1 month after the surgery were included. [10]

An anonymized database of age, sex, diabetic status, refractive status, use of antifibrotic agents, lens status at the onset of the BRI, bleb leakage, oozing, intraocular pressure (IOP), infection stage, prophylactic use of antibiotics/steroids,

and treatment methods of antibiotics was created.

We examined whether bleb leakage, oozing, and the IOP were involved in the recurrence of BRIs by examining the data before and after the initial BRI.

Each infection was classified into three stages. [11-13] Stage I was when the infection was localized to the bleb site without cells in the anterior chamber, Stage II was when the infection extended into the anterior chamber but not into the vitreous, and Stage III was when the infections also involved the vitreous.

A stage-by-stage treatment protocol has been proposed for the treatment of bleb infections.[14] In Stage 1, aggressive fluroquinolone eyedrops and/or subconjunctival injection of vancomycin and ceftazidime are given. In Stage 2, a strengthening of the topical therapy is recommended, but the effectiveness of systemic antibiotics has not been documented.[15] In Stage 3, pars plana vitrectomy with injection of intravitreal antibiotics is immediate given.[16] The medical and surgical treatments were based on the protocol (above) which were determined by the treating physician according to the opinion of infectious disease experts. All eyes were intensively treated with antibiotics and surgery when indicated. Antibiotic therapy consisted of either topical

and/or systemic antibiotics, subconjunctival, intracameral, and intravitreal treatments. The surgical treatment included pars plana vitrectomy.

Cases in which antibacterial topical drops were applied on a daily basis were defined as prophylactic antibacterial drug administration cases. The frequency of antibacterial topical drops varied, e.g., appropriate use and regular eye drops. Similarly, the duration of use varied.

The primary endpoint was a recurrence of a BRI that was defined as at least two episodes of bleb purulence with or without intraocular inflammation that occurred at intervals of three months or more. [9] Earlier studies have confirmed that there is a period of complete resolution between the initial infection and the recurrence. [9] The time when the conjunctival hyperemia was not detected and the anterior chamber was confirmed to be quiet was defined as the resolution time of the BRI. [17] Because the purpose of this study was to determine risk factors for recurrences, we analyzed the data obtained at the initial onset of the BRI of each eye. In the recurrence cases, we examined whether there was a bacteriological relationship between the first and recurrent BRIs of each eye.

Bleb leakage and transconjunctival oozing were evaluated by fluorescein staining and observing the bleb under cobalt blue slit-lamp illumination. No detailed observation time has been set for the evaluation of transconjunctival oozing.

Hypotony was defined as an IOP ≤5 mmHg as designated by the World Glaucoma Association's Guidelines on Design and Reporting of Glaucoma Surgical Trials. [18]

Statistical analyses

The baseline characteristics of the patients are presented as the median and interquartile range (IQR) for continuous variables, and numbers (%) for categorical variables. The recurrence of infections was considered to be independent events in the analysis. Kaplan-Meier estimation was performed to estimate the recurrence-free survival rate for each suspected factor. Log-rank tests and Cox proportional hazards analyses were performed to identify the factors significantly associated with the recurrence of a BRI. Cox proportional hazards analysis was performed both unadjusted and adjusted for age or bleb leakage. A two-sided P <0.05 was taken to be statistically significant. All statistical analyses were performed with the R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). [19]

Results

A total of 135 BRIs developed in 112 eyes of 107 patients. One patient was excluded because the eye required enucleation as a treatment for the initial BRI. Two other patients were excluded because the BRI developed one month after the glaucoma operation. Another patient was excluded because the date of onset was not posted. The data of the 21 infections with a second infection and 2 infections after a third infection were bacteriologically investigated. In the end, 108 eyes of 103 patients were analyzed (Figure 1), and the demographics of the participants are shown in Table 1.

Initial bleb-related infection

The median age of the patients at the onset of the initial BRI was 59 years (IQ, 41 to 69 years). There were 61 men and 42 women, and 11 (10.7%) of these patients were diabetic. The types of glaucoma were; primary open-angle glaucoma in 38 (35.2%), normal-tension glaucoma in 15 (13.9%), primary angle-closure glaucoma in 3 (2.8%), developmental glaucoma in 27 (25.0%), secondary glaucoma in 24 (22.2%), and congenital glaucoma in 1 (0.9%). More information of the eyes with secondary glaucoma is presented in Table 1.

The median refractive error (spherical equivalent) was -2.25 diopters (D; IQR -7.00 to 0.50 D). The median interval from the glaucoma surgery to the onset of the initial BRI was 6.3 years (IQ, 3.20 to 10.77 years), and the time from the resolution of the initial BRI to the date of last consultation or the date of the recurrence BRI was 5.58 years (IQ, 1.38 to 11.54 years). Ninety-six eyes (89.7%) had been treated with intraoperative MMC, 9 eyes (8.4%) with 5-FU, and 2 eyes (1.9%) without any antifibrotic agent. The amount of MMC was 0.02 mg in 1 (0.9%), 0.03 mg in 1 (0.9%), 0.05 mg in 1 (0.9%), 0.1 mg in 75 (69.4%), and 0.2 mg in 18 (16.7%). The concentration of the injected MMC was 0.04% in all cases.

The bleb morphology was cystic in 94 (88.7%) eyes, diffuse in 11 (10.4%) eyes, and flat in 1 (0.9%) eye. The bleb was avascular in 96 (89.7%) eyes, hypo-vascular in 10 (9.3%) eyes, and hypervascular in 1 (0.9%) eye. There was no description of the bleb morphology in 2 eyes and of the vascular distribution in 1 eye.

The lens status at the onset of BRI was phakia in 75 eyes (69.4%), aphakia in 9 eyes (8.3%), and an implanted intraocular lens in ~~9~~24 eyes (22.2%). There were 27 eyes that underwent cataract surgery prior to the trabeculectomy, and an intraocular lens

was implanted in 18 eyes. Trabeculectomy combined with cataract surgery was performed on 9 eyes, and an intraocular lens was implanted in 6 eyes. Twelve eyes (11.1%) underwent bleb revision surgery prior to the onset of the initial BRI.

The conjunctival suture was exposed in three eyes (2.8%) before the onset of the initial BRI, and these eyes had no recurrence after the initial BRI was resolved. One eye required bleb revision after the initial BRI improved because the function of the bleb decreased. Five eyes underwent conjunctival suture or amnion transplantation after the initial BRI episode, and a recurrence of a BRI was observed in one of these eyes. One eye had the conjunctival suture exposed after the second BRI episode, and no recurrence was observed thereafter.

Fifty-two (48.1%) eyes had bleb leakage at the onset of the BRI, and 33 eyes (33.7%) had leakage after the initial BRI improved. Transconjunctival oozing was observed in 7 (7.0%) eyes at the onset of the BRI and in 8 (8.2%) eyes had after the initial BRI improved.

The median IOP at the onset of a BRI was 9.0 mmHg (IQR, 5.0 to 12.5 mmHg), and it was not posted in 5 eyes. Thirty eyes developed ocular hypotony with an IOP ≤5

mmHg at the onset of the BRI. After a resolution of the initial BRI, the median IOP at the onset of BRI was 10.0 mmHg (IQR, 7.0 to 14.0 mmHg), and hypotony was present in 12 eyes (12.5%).

The disease severity at the time of diagnosis was Stage I in 65 (60.2%) eyes, Stage II in 20 (18.5%) eyes, and Stage III in 23 (21.3%) eyes.

All eyes were intensely treated with antibiotics based on the advice of an infectious disease experts. Topical antibiotic eye drops were used in all eyes. A subconjunctival injection of antibiotics was performed in 32 Stage Ⅰ (49%) eyes, in 15 Stage Ⅱ (75%) eyes, and in 19 Stage Ⅲ (83%) eyes. An intracameral injection of vancomycin and ceftazidime was given in 6 Stage Ⅱ eyes (30%), and an intravitreal injection of vancomycin in 3 Stage Ⅱ eyes (15%).

Vitreous surgery was performed on 22 Stage Ⅲ eyes (96%) and in 8 Stage Ⅲ eyes (35%). Vancomycin and ceftazidime were administered intravitreally after vitreous surgery or were added to the perfusion fluid during surgery, and in 1 Stage Ⅲ eye (4%), and vancomycin and amikacin were administered intravitreally after surgery.

Systemic antibiotics were given to 45 Stage Ⅰ eyes (69%), 19 Stage Ⅱ eyes (95%), and 23 Stage Ⅲ eyes (100%).

Recurrent bleb-related infections

A recurrent BRI developed in 21 eyes of 21 patients (13 men, 8 women). Two patients developed a third episode of BRI at 7 and 27 months after the second infection.

The cultured pathogens detected in eyes with recurrent infections were diverse (Table 2). *Staphylococcal species* were isolated in 14 cases of *Staphylococcus aureus* including 5 cases of methicillin resistant *S. aureus*, and 9 cases of coagulase negative staphylococcus including methicillin resistant, *Staphylococcus epidermidis*. *Streptococcus* species were isolated in 7 cases. *Corynebacterium, Rothia mucilaginosa, Moraxella catarrhalis,* and *Cutibacterium acnes* were detected in 1 case each. *M. catarrhalis* and *C. acnes* were isolated in the same culture of 1 eye.

The cultures were negative in 18 BRIs in the recurrent eyes. Cultures were not obtained from three episodes. The infecting organism that was isolated at the time of

the recurrent infection was the same as the ones isolated from the initial infection in Case 20 (Table 2: *S. epidermidis*).

The stage of the infections, whether vitreous surgery was performed, and changes in visual acuity before and after treatment are shown in Table 2. The presence or absence of bleb leakage and hypotony before each BRI are also presented in Table 2.

Significance of correlations between each risk factor and recurrence of BRI

Kaplan-Meier estimation showed that there was no significant difference in the recurrence of BRIs between the patients who were ≤60 years to those >60 years for up to ten years. The threshold age was defined by the median value. There were no significant differences in the sex distribution, status of diabetes, lens status at the onset, refractive error, morphology of the bleb, vascularity of the bleb, use of antifibrotic agents, prophylactic use of steroid eye drops, bleb leakage at the onset of the initial BRI, oozing at the onset of the initial BRI, oozing after the resolution of the initial BRI, hypotony after the resolution of the initial BRI, infection stage, bleb revision before the initial BRI, and antibiotic therapy for up to ten years.

The recurrence-free rate in cases with hypotony at the onset of the initial BRI was 0.522 (95% confidence interval [CI]: 0.288–0.712) which was significantly lower than cases without hypotony at 0.833 (95%CI: 0.669–0.921) at the 10 years follow-up time (*P* = 0.004, log-rank test Figure 2). The recurrence-free survival rate for the eyes with prophylactic use of topical antibiotics was 0.659 (95%CI: 0.495–0.782) which was significantly lower than that of eyes without use at 0.941 (95%CI: 0.650–0.991) at the 10 years follow-up time (*P* = 0.046, log-rank test Figure 3). The recurrence free rate in cases with bleb leakage after the resolution of the initial BRI was 0.660 (95% confidence interval [CI]: 0.441-0.810) which was significantly lower than cases without bleb leakage after the resolution of the initial BRI at 0.893 (95%CI: 0.760-0.955) at the 10 years follow-up time (*P* = 0.021, log-rank test Figure 4).

The hazard ratios were calculated to determine which factors were significantly associated with the recurrence of BRIs. The factors examined by univariate Cox proportional hazards regression analysis are shown in Table 3. Ocular hypotony at the onset of the initial BRI and bleb leakage after the resolution of the initial BRI were identified as significant risk factors for the recurrence of BRI (ocular hypotony: Hazard ratio [HR]: 0.301; 95% CI: 0.126–0.716; *P* = 0.007; bleb leakage: HR: 2.882;

95% CI: 1.129-7.354; *P* = 0.027). The other factors were not significantly associated with recurrence of BRIs by univariate analysis (all *P* >0.05).

The Cox proportional hazards model adjusted for age confirmed that ocular hypotony at the onset of the initial BRI and bleb leakage after the resolution of the initial BRI were significantly associated with the recurrence of BRIs (ocular hypotony: HR: 0.266; 95% CI: 0.111–0.641; *P* = 0.003; bleb leakage HR: 3.137; 95% CI: 1.206-8.162; *P* = 0.019). Similar to the univariate Cox proportional hazards regression findings, the other factors were not significantly associated with the recurrence of BRIs (all, *P* >0.05). The Cox proportional hazards model adjusted for bleb leakage at the onset of the BRI or refractive error showed that hypotony at the onset of the BRI was significantly associated with the recurrence of a BRI (HR: 0.333; 95% CI: 0.138-0.805*; P* = 0.015, HR. 0.362; 95% CI: 0.147-0.895*; P* = 0.028). The Cox proportional hazards model adjusted for hypotony after the resolution of the BRI or the refractive error showed that bleb leakage after the resolution of the BRI was significantly associated with the recurrence of a BRI (HR: 2.989; 95% CI: 1.155-7.739*; P* = 0.024).

Discussion

Earlier studies have identified several factors that were significantly correlated with a recurrence of a BRI. The major factors were the use of antifibrotic agents, [20] the presence of bleb leakage, [8, 21-24] a younger age, [2, 24] and a thin-walled avascular bleb. [2,3] Our results showed that the use of antifibrotic agents, age, morphology of the bleb, vascularity of the bleb, and bleb revision before the initial BRI were not significant risk factors for recurrences of BRIs (Table 3).

Kaplan-Meier estimation analyses for the recurrence of BRI showed that the eyes treated by MMC tended to develop recurrences of BRI at significantly higher rates than eyes treated with 5-FU. This may be because the eyes treated with MMC had longer follow-up times than those treated with 5-FU. In addition, the number of cases using 5-FU was only 9 eyes, and this low number may have contributed to the lack of statistical significance. Thus, with our data, the use of antifibrotic agents was not a statistically significant factor for a recurrence of a BRI.

Most of blebs were cystic and hypovascular, and we suggest that this was because this study was conducted on eyes that developed a BRI. The grading system for the classification of the blebs may be used [25] [Cantor LB J Glaucoma 2003], but this

study included older cases. Therefore, only the morphological evaluations and the blood vessel distributions were described in the evaluations of the blebs.

Although there have been reports [2,3] that the morphology and vascularity of the blebs are factors that lead to the development of BRIs, our findings did not find significant differences in the bleb morphology or vascularity in eyes that had a recurrence BRI.

Our results confirmed that ocular hypotony at the onset of the initial BRI was significantly correlated with recurrences of a BRI (Figure 2, Table 3). However, no significant correlation was found between the presence of hypotony after the resolution of the BRI and the recurrence of a BRI. Kim et al. [26] reported that an intraocular pressure below the target pressure was a risk factor for a BRI, and Higashide et al. [27] reported that BRI was associated with persistent hypotony. However, these studies were not designed specifically to determine the cause of a recurrence of a BRI. To the best of our knowledge, there have not been any reports that statistically confirmed a significant relationship between the recurrence of a BRI and hypotony. However, a significant relationship was found between hypotony at the onset of the initial BRI and the recurrence of a BRI in our cohort.

There have been several reports that bleb leakage is associated with a BRI. [8, 21-24, 27] Our Kaplan-Meier estimation comparing the eyes with bleb leakage after the resolution of the initial BRIs to those without leakage showed that the cases with leakage were significantly corelated with the recurrence of BRIs.

The presence of bleb leakage lowers the IOP, so it can be inferred that leakages and ocular hypotony should be correlated. Cox analysis adjusted for hypotony and bleb leakage was performed to examine whether these factors were correlated to each other. This statistical examination was made for each period before and after the BRIs. The results showed that hypotony at the onset of BRI and bleb leakage after the resolution of the BRI were significant risk factors for BRIs and that each factor is an independent risk factor for the recurrence of a BRI.

Conjunctival sutures are an effective means of stopping leakages and preventing the development of a BRI [26]. Because the number of conjunctival sutured cases before the initial BRI was few, statistical analysis on the effects of conjunctival sutures were not meaningful. In 1 of 5 eyes, the infection recurred after the conjunctival suture or amnion transplantation was used after the initial BRI.

In 21 eyes that had a recurrent BRI, bleb leakage was observed before the initial BRI in 15 of these eyes, and the leakage continued after the initial BRI in 8 eyes. Although no leakage was observed at the time of initial infection, the leakage appeared after the treatment in 4 eyes. Considering that the leakage after the treatment for initial BRI was significantly correlated with the recurrence of a BRI, treatments for leakage should be actively performed.

Transconjunctival oozing was usually found when the avascular area of the filtering bleb is wide [28,29] and the wall of is thin. [28,30] It has been suggested that transconjunctival oozing may be present before bleb leakage occurs [29] and that oozing may be correlated with the onset of a BRI [30].

Although our results showed a significant association between hypotony and a recurrence of a BRI, consideration should be given to the possibility that the factors of oozing may be involved because cases with oozing tend to have lower IOP and are associated with hypotony [28,30]. Oozing was not found to be a significant risk factor of recurrence, but it should be considered that transconjunctival oozing was not examined with observation criteria. Considering that most of the blebs were

avascular and bleb leakage that were found in 52 eyes (48.1%) at the onset of the BRI and in 33 eyes (33.7%) after the resolution of the BRI, oozing could have been identified in more cases with observation criteria.

Jampel et al. reported that the chronic use of topical antibiotics increased the likelihood of BRIs due to the alterations of the conjunctival flora.[20] However, Waheed et al.[9] did not confirm this. Our Kaplan-Meier estimation results showed that the prophylactic use of antibiotics significantly increased the risk of recurrent BRIs during the ten-year follow-up period (Figure 3). However, the Cox proportional hazards regression analysis did not detect a significant difference (Table 3). The regular use of antimicrobial eye drops was not involved in the prevention of BRI but it had an effect on the bacterial flora. Therefore, we suggest that the regular use of antibacterial eye drops should be avoided. After the resolution of the initial BRI, prophylactic use of antibiotics was continued in 92 eyes (85.2%). Due to the bias of the data, statistical examination on the prophylactic use of antibiotics after the resolution of the initial BRI could not be performed.

In the cases of recurrences, only one case had the same causative organism as the original infection. In most cases, the causative organism was different between the

initial and recurrence cases (Table 2) although there were many false negative eyes. Waheed et al. [9] reported little uniformity in the microbiological spectrum of the cultured organisms at the time of the initial and recurrent infections. Similar results were obtained in this study.

Yamamoto et al reported that Stage 3 BRIs cause significant reduction of vision [8]. The changes in the visual acuity were not statistically examined by stages because of the small number of eyes. In Case 21, a rapid decrease in the visual acuity was observed even though the second BRI was at Stage 1 (Table 2). The central visual field disorder of this eye was serious before the onset of the second infection, and it was not measurable due to the infection. This resulted in a sudden decrease in the visual acuity. We suggest that in cases with slight visual field alterations, aggressive treatment be instituted even if the BRI stage is mild.

Our study has several limitations. First, this was a retrospective study in a single institution. Therefore, a patient selection bias cannot be ruled out. Second, the number of recurrent cases was low. Because this study was not conducted by statistically determining the required number of cases, future studies are needed to confirm our findings. Third, insufficient description in the past medical records

prevented us to obtain important and relevant clinical findings, such as blepharitis that can alter the ocular surface. We cannot eliminate the fact that there may be cases where oozing was overlooked due to lack of strict observation criteria.

In conclusion, the prophylactic use of topical antibiotics at the onset of BRI, ocular hypotony at the onset of BRI, and bleb leakage after the resolution of a BRI were found to be risk factors for the recurrence of BRIs. Special attention with carefully check for leakage and frequent follow-ups are required for eyes after a resolution of a BRI. Treatment for leakage should be actively performed.

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Figure legends

Figure 1. Flow diagram of experimental procedures.

Flow chart showing the number of infections enrolled and analyzed. BRI = Bleb-related infection.

Figure 2. Hypotony. Cumulative recurrence-free survival rate of BRI determined by a Kaplan-Meier estimation. Thirty eyes with hypotony with intraocular pressure (IOP) ≤5 mmHg, and 73 eyes without hypotony and IOP unknown in 5 eyes. The recurrence-free survival rate for eyes with hypotony is 0.522 [0.288-0.712] and for eyes without hypotony was 0.833 [0.669-0.921] at the 10 years follow-up (cumulative probability [95%CI]).

Figure 3. Prophylactic use of antibiotics.

Cumulative recurrence-free survival rate of BRI calculated by a Kaplan-Meier estimation. Subjects are 81 eyes with use of antibiotics, and 26 eyes without it, and unknown in 1 eye. The recurrence-free survival rate for eyes with use of antibiotics is 0.659 [0.495-0.782] and for eyes without use of antibiotics is 0.941 [0.650-0.991] at the 10 years follow-up (cumulative probability [95%CI]).

Figure 4. Bleb leakage after the resolution of the initial BRI.

Cumulative recurrence-free survival rate of bleb-related infection calculated by Kaplan-Meier estimation. Subjects are 33 eyes with bleb leakage, and 65 eyes without it, and unknown in 10 eyes. The recurrence-free survival rate for eyes with bleb leakage after the resolution of the initial BRI is 0.660 [0.441-0.810] and for eyes without it is 0.893 [0.760-0.955] at the 10 years follow-up (cumulative probability [95% CI]).