Bleb-related infection after primary trabeculectomy: medical chart reviews from 1993 to 2021

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ABSTRACT

Background To investigate the incidence of and risk factors for bleb-related infection (BRI) in patients who underwent mitomycin C-augmented primary trabeculectomy.

Methods We reviewed the medical charts of consecutive patients who had received primary trabeculectomy in Taipei Veterans General Hospital. We recorded the demographic and clinical characteristics of patients before, during and after surgery. Furthermore, we recorded the time interval between surgery and infection onset, clinical manifestations and visual outcomes of patients with BRI. The cumulative incidence of BRI was estimated using the Kaplan-Meier method. A Cox proportional hazards model was used to explore factors associated with BRI.

Results In total, 1663 eyes were postoperatively followed up for 94.57±65.23 months. The cumulative incidence of BRI was 1.86 per 1000 person-years during the 28-year follow-up period: 24 (1.44%) patients developed BRI and 6 (0.36%) patients additionally developed endophthalmitis. A multivariate analysis revealed a significant association of BRI with wound manipulation, high myopia and hyperlipidaemia. Patients younger than 60 years were more likely to receive wound manipulation than their elderly counterparts (<0.001). One year after BRI, the best corrected visual acuity of the eyes with blebitis did not change significantly, whereas that of the eyes with endophthalmitis worsened significantly.

Conclusion Risk factors for BRI after trabeculectomy include wound manipulation, high myopia and hyperlipidaemia. Considering myopia is highly prevalent throughout the world and is a risk factor for glaucoma, the lifelong risk of BRI after trabeculectomy in eyes with high myopia warrants the attention of ophthalmologists.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Well-known risk factors for bleb-related infection (BRI) include use of supplement antimetabolites and wound manipulation.

WHAT THIS STUDY ADDS

⇒ Chart review of 1663 eyes receiving mitomycin C-augmented trabeculectomy from 1993 to 2021 did not find a higher incidence of BRI than those from studies without antimetabolites usage. Besides wound manipulation, high myopia and hyperlipidaemia were also associated with BRI, which have not been reported.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Prudent use of antimetabolites in trabeculectomy may help minimise the BRI event. Patients with a history of trabeculectomy should be reminded to well control their dyslipidaemia and ophthalmologists should remain alert to a thin bleb in eyes with high myopia.

INTRODUCTION

Glaucoma filtration surgery is usually performed when conservative treatment fails to control the intraocular pressure (IOP) or to halt the deterioration of glaucomatous optic neuropathy. Despite the development of numerous novel minimally invasive glaucoma surgeries in recent years, most surgeons prefer trabeculectomy when low-teen IOP is the target pressure.[1] However, patients who receive trabeculectomy have a lifelong risk of bleb-related infection (BRI) because it can develop within days or even after years of surgery.[2] Patients and ophthalmologists must be alert to the early presentation of BRI because it may rapidly lead to vision-threatening endophthalmitis.

The incidence of and risk factors for BRI vary across different studies due to variations in the duration of postoperative follow-up time, study design and race.[3–6] Mitomycin C (MMC) use is a well-known risk factor for BRI; the incidence of BRI increases from 0.2%–1.5% in non-augmented glaucoma filtering surgery to 1.5%–13.8% in MMC-augmented trabeculectomy.[3–5] Nevertheless, Rai *et al* from Moorfields Eye Hospital reported that cumulative incidence of BRI after MMC introduction in trabeculectomy reduced from 5.7% in the mid-1990s to 1.2% post-1999.[6] The authors attributed BRI reduction to accumulated experience in MMC application and the evolution of surgical approaches and techniques in trabeculectomy.

Furthermore, younger age has been reported to be a risk factor for BRI.[7 8] A retrospective study showed that the mean age of Asian patients receiving trabeculectomy was lower than that of their Western counterparts.[9] In addition, several studies have reported a trend of increasing prevalence and incidence of glaucoma even in the young population.[10 11] Reasons for an increased incidence of BRI in young patients are not clear, which deserve further evaluation considering that young patients are the main workforce in

the society, and BRI may result in great impact on patients and their family members.

We conducted this retrospective cohort study spanning 28 years to determine the incidence of and risk factors for BRI in patients who had received primary trabeculectomy augmented with MMC in our hospital.

MATERIALS AND METHODS

Study population and data collection

We reviewed the medical charts of consecutive patients who had received primary trabeculectomy in Taipei Veterans General Hospital between 1 January 1993 and 30 April 2021. Patients who had received primary trabeculectomy in other hospitals, had a history of ocular surgery that had perturbed the superior conjunctiva or had postoperative follow-up duration<90 days were excluded from this study. We recorded the following data of patients: sex, age and lens status during primary trabeculectomy, glaucoma type, concentration and duration of intraoperative MMC application, presence/absence of high myopia, presence/absence of postoperative wound manipulation, subsequent reoperations and concurrent systemic diseases.

High myopia was defined as the axial length of ≥26.5 mm for pseudophakic eyes or the mean spherical equivalent of ≥6 dioptres for phakic eyes.[12] None of the patients in the study had undergone laser refractive surgery. Wound manipulation was defined as any surgical intervention to modify the filtration bleb, such as transconjunctival revision with a needle or bleb knife, conjunctival wound resuture, compression suture, sclera graft or amnion membrane graft, after primary trabeculectomy. Reasons for wound manipulation can be further categorised into four groups: for better IOP control, for bleb at risk, for hypotony or bleb leak and for other reasons. Bleb at risk was defined as thin avascular cystic bleb with negative Seidel test. Hypotony was defined as IOP<6 mm Hg with signs of hypotony such as hypotony maculopathy or choroidal detachment. In patients with systemic comorbidities, we defined hypertension, diabetes and hyperlipidaemia based on the patient's self-report or information stored in the national health insurance ID card, which showed medications the patient was taking to treat the diseases mentioned above. Cardiovascular disease was defined as having any history of myocardial infarction and/or cerebral vascular event, and history of catheterisation intervention, stenting and coronary artery bypass graft.

For patients with BRI, the time interval from symptom onset to hospital admission, symptom presentation, time interval between primary trabeculectomy and infection onset, lens status at presentation, culture site, culture results and treatment course were recorded. Furthermore, the best corrected visual acuity (BCVA) and IOP at the last visit before infection, at infection presentation and 1 year after treatment were recorded. BCVA values were converted into logMAR values for calculation. The measurements of visual acuities beyond the limits of the Snellen chart, namely based on counting fingers, hand movement, light perception and no-light perception were 1.9, 2.3, 2.7 and 3, respectively, in logMAR numbers.[13]

Definition of BRI

BRI was defined as ocular pain and the presence of mucopurulent material within and around conjunctival blebs, with the loss of bleb translucency, conjunctival congestion that is prominent around the bleb, and cells in the anterior chamber. Endophthalmitis was defined as additional findings of hypopyon or inflammatory cells or opacity in the vitreous body.[14] Early-onset BRI was defined as BRI onset within 1 month of surgery, and late-onset BRI was defined as BRI onset>1 month after surgery.[15]

Causative pathogens were identified through the culture of conjunctival eye swab, aqueous aspiration from the anterior chamber or vitreous aspiration at the discretion of the physician in charge.

Statistical analysis

SPSS statistical software V.22.0 and STATA statistical software V.15.1 (StataCorp, College Station, Texas, USA) were used for statistical analysis. Categorical and continuous data of patients with and without BRI were compared using the χ^2 and Mann-Whitney tests, respectively. The cumulative incidence of BRI was estimated using the Kaplan-Meier method. A Cox proportional hazards model was used to explore factors associated with BRI. Baseline demographic (age and sex) and clinical (glaucoma type, concentration and duration of applied MMC, wound manipulation, reasons for wound manipulation, repeat glaucoma surgery, presence of high myopia and systemic disease) factors with a p value of <0.1 in the univariate model were included in the multivariate analysis. Hazard ratios and 95% CIs for BRI risks were calculated. Furthermore, we compared the characteristics of patients with blebitis and those with endophthalmitis. All statistically significant levels were set at a two-tailed p<0.05.

Table 1 Baseline characteristics of patients with or without bleb-related infection (BRI)

Characteristics	Total n=1663	BRI n=24	No BRI n=1639	P value*
Median age (range)	63 (7–95)	51 (11–87)	63 (7–95)	0.008
Age≥60 years, n (%)	967 (58.1)	8 (33.3)	959 (58.5)	0.013
Male, n (%)	1067 (64.2)	17 (70.8)	1050 (64.1)	0.492
Type of glaucoma				0.087
POAG, n (%)	826 (49.7)	17 (70.8)	809 (49.4)	
PACG, n (%)	503 (30.2)	3 (12.5)	500 (30.5)	
Others, n (%)	334 (20.1)	4 (16.7)	330 (20.1)	
Repeat trabeculectomy†, n (%)	221 (13.3)	8 (33.3)	213 (13.0)	0.009
Subsequent Ahmed valve implant, n (%)	40 (2.4)	0 (0.0)	40 (2.4)	0.105
Wound manipulation (WM), n (%)				<0.001
No WM	1353 (81.4)	9 (37.5)	1344 (82.0)	
WM for intraocular pressure control	273 (16.4)	6 (25.0)	267 (16.3)	
WM for bleb at risk‡	12 (0.7)	8 (33.3)	4 (0.2)	
WM for hypotony/bleb leak	22 (1.3)	1 (4.2)	21 (1.3)	
Others	3 (0.2)	0 (0.0)	3 (0.2)	
High myopia, n (%)	158 (9.5)	9 (37.5)	149 (9.1)	<0.001
MMC concentration, mg/mL				0.309
≤0.2, n (%)	576 (39.1)	12 (50.0)	564 (39.0)	
0.25–0.3, n (%)	718 (48.8)	8 (33.3)	710 (49.0)	
>0.3, n (%)	178 (12.1)	4 (16.7)	174 (12.0)	
Comorbidities				
Diabetes mellitus, n (%)	344 (20.7)	6 (25.0)	338 (20.6)	0.612
Hypertension, n (%)	572 (34.4)	10 (41.7)	562 (34.3)	0.450
Hyperlipidaemia, n (%)	83 (5.0)	6 (25.0)	77 (4.7)	0.001
Cardiovascular disease, n (%)	198 (11.9)	5 (20.8)	193 (11.8)	0.194

*P value in this table is calculated to compare patients with and without BRI.
†Repeat trabeculectomy is defined as subsequent surgery performed before the event of BRI.
‡Bleb at risk denotes thin avascular cystic bleb without leak.
MMC, mitomycin C; n, number of eyes; Others, inflammatory glaucoma, neovascular glaucoma, steroid induced glaucoma…etc; PACG, primary angle closure glaucoma; POAG, primary open angle glaucoma.

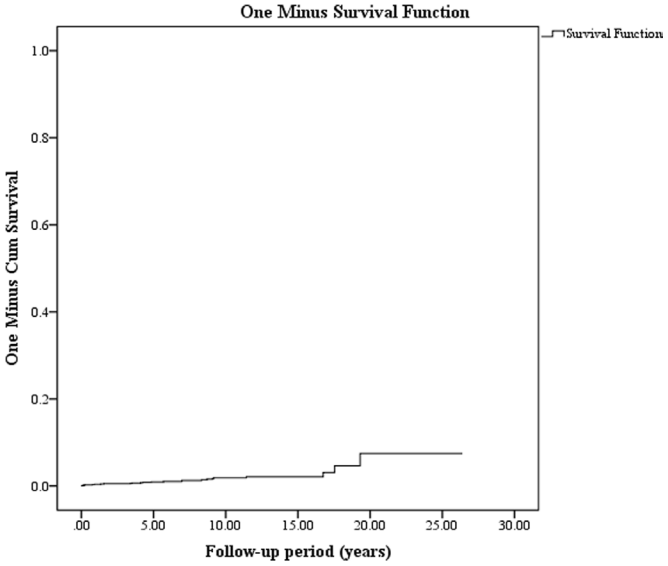

Figure 1 Kaplan-Meier estimates for the cumulative incidence of bleb-related infection developing after mitomycin C-augmented primary trabeculectomy.

RESULTS

We evaluated 2040 patients (2566 eyes) who had received MMC-augmented primary trabeculectomy during the study period. Among these, 903 eyes were excluded for the following reasons: 182 eyes had a history of glaucoma surgery (including trabeculotomy, trabeculectomy and XEN45 gel stent implant), 527 eyes had a previous surgery involving superior conjunctiva (including extracapsular cataract extraction and scleral tunnel approach phacoemulsification) and 194 cases were lost to follow-up within 90 days of surgery. Finally, we included 1663 eyes of 1354 patients in the final statistical analyses.

Characteristics of the study population

The postoperative follow-up period averaged 94.57±65.23 months (mean±SD) and ranged from 3 to 321.27 months. Table 1 shows the baseline characteristics of all the eyes studied. The median age at primary trabeculectomy, proportion of eyes receiving wound manipulation or subsequent repeat trabeculectomy, proportion of eyes with high myopia, and proportion of participants with hyperlipidaemia were significantly different between the BRI and non-BRI groups.

Cases with BRI

Among the patients enrolled into this study, 24 (1.44%) and 6 (0.36%) developed BRI and endophthalmitis, respectively. The cumulative incidence of BRI was 1.86 per 1000 person-years during the 28-year follow-up (figure 1). None of the participants had multiple BRI events.

The most common chief complaint of the patients studied was ocular pain (12 patients, 50%) and red eye (12 patients, 50%), followed by blurred vision (5 patients, 21.83%), purulent discharge (5 patients, 20.83%) and tearing (2 patients, 8.33%). The mean interval between primary trabeculectomy and BRI onset was 73.63±67.74 months, ranging from 15 days to 19 years. In this study, 1 (4.17%) and 23 (95.83%) patients developed early-onset and late-onset BRI, respectively. The interval between symptom onset and medical intervention was 4 days on average in the blebitis group and 2.83 days in the endophthalmitis group.

In total, 13 (54.17%) patients had positive culture results, with the causative bacteria being *Staphylococcus aureus* (4 patients),

Table 2 Risk factors of BRI after primary trabeculectomy

	Univariate analysis		Multivariate analysis*	
Predictive variables	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value***
Age≥60 years†	0.38 (0.16 to 0.90)	0.028	1.04 (0.38 to 2.85)	0.936
Sex (male)	1.40 (0.58 to 3.38)	0.454		
Type of glaucoma				
POAG	Reference			
PACG	0.28 (0.08 to 0.95)	0.040	0.91 (0.22 to 3.69)	0.892
Others	0.70 (0.24 to 2.10)	0.526	1.16 (0.35 to 3.80)	0.812
Repeat trabeculectomy‡	2.27 (0.95 to 5.41)	0.065	2.24 (0.84 to 5.98)	0.108
Wound manipulation (WM)				
No WM	Reference			
WM for intraocular pressure control	3.53 (1.26 to 9.93)	0.017	3.06 (1.03 to 9.05)	0.044
WM for bleb at risk§	66.51 (25.29 to 174.90)	<0.001	36.27 (12.23 to 107.61)	<0.001
WM for hypotony/bleb leak	7.76 (0.98 to 61.34)	0.052	8.81 (1.06 to 73.25)	0.044
Others	–	0.988	–	
High myopia	5.76 (2.52 to 13.19)	<0.001	3.50 (1.27 to 9.70)	0.016
Comorbidities				
Diabetes mellitus	1.50 (0.60 to 3.79)	0.390		
Hypertension	1.36 (0.60 to 3.06)	0.461		
Hyperlipidaemia	6.37 (2.52 to 16.07)	<0.001	5.83 (2.08 to 16.40)	0.001
Cardiovascular disease	1.83 (0.68 to 4.89)	0.231		

*All factors with p<0.1 in the univariate analysis were included in the Cox multivariate analysis.
†Age in this table is defined as the age at primary trabeculectomy.
‡Repeat trabeculectomy is defined as subsequent trabeculectomy performed before the event of BRI.
§Bleb at risk denotes thin avascular cystic bleb without leak.
Others, inflammatory glaucoma, neovascular glaucoma, steroid induced glaucoma…etc; PACG, primary angle closure glaucoma; POAG, primary open angle glaucoma.

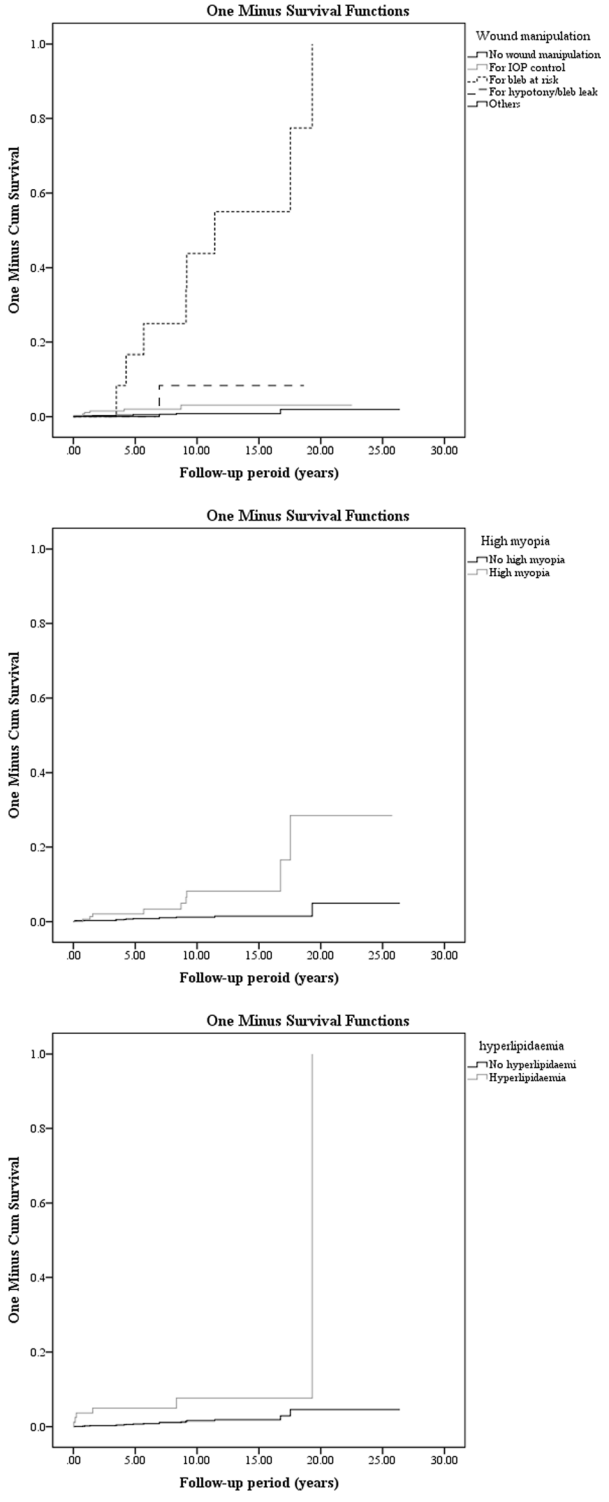

Figure 2 (Top) Kaplan-Meier estimates for the incidence of bleb-related infection (BRI) developing in cases with and without wound manipulation for intraocular pressure (IOP) control, for bleb at risk, for hypotony or bleb leakage and others. (Middle) Kaplan-Meier estimates for the incidence of BRI developing in cases with high myopia and without high myopia. (Bottom) Kaplan-Meier estimates for the incidence of BRI developing in cases with hyperlipidaemia and without hyperlipidaemia.

Enterococcus species (3 patients), *Propionibacterium acnes* (2 patients), *Enterococcus faecalis* (1 patient), *Streptococcus pneumoniae* (1 patient), *Staphylococcus hominis* (1 patient) and *Burkholderia cepacia* (1 patient). Positive culture results were obtained from eye swabs of 12 patients and both aqueous humour and eye swabs of 1 patient. All patients with BRI were treated with aggressive topical antibiotics covering a broad spectrum of species before the culture results were revealed. Systemic antibiotics and surgical treatment were administered to selected patients according to disease severity.

Risk factors of BRI

A multivariate analysis revealed that wound manipulation, high myopia and hyperlipidaemia had a p value of <0.05 after adjusting for other variables with $p<0.1$ in the univariate analysis (table 2). Because wound manipulation is performed for various reasons, we further conducted a subgroup analysis and found that the BRI risk is significant in each subgroup (table 2). However, the BRI risk of the bleb at risk subgroup (adjusted HR 36.27, 95% CI 12.23 to 107.61, $p<0.001$) was remarkably higher than that of the other subgroups (table 2). The cumulative incidence of BRI of each risk subgroup is presented in figure 2.

Comparisons between patients with blebitis and those with endophthalmitis

The results were summarised in table 3. One year after the BRI event, the BCVA of the endophthalmitis eyes deteriorated significantly, whereas that of the blebitis eyes remained relatively constant ($p=0.001$). The mean IOP of both subgroups remained controlled 1 year after the BRI event, but the number of glaucoma medication tended to increase more in the endophthalmitis group than in the blebitis group (table 3). Patients with endophthalmitis appeared to have a greater proportion of hyperlipidaemia than those with blebitis alone ($p=0.038$).

DISCUSSION

In this retrospective study, we showed that the cumulative incidence of BRI is 1.86 per 1000 person-years in a cohort of 1663 eyes that received MMC-augmented primary trabeculectomy from 2003 to 2021. To the best of our knowledge, this study included one of the largest cohorts among the studies on BRI in Asians published in English language. In addition to wound manipulation, which has been repeatedly reported to be a risk factor for BRI, myopia and hyperlipidaemia were associated with BRI occurrence in our study.

Although earlier studies have reported that the adjunction of MMC to trabeculectomy increases BRI risk from 8-fold to 10-fold,[3–5] our study results are comparable with the results reported by Rai *et al*, where the cumulative incidence of BRI was 1.2% in a cohort of 764 eyes receiving MMC trabeculectomy in a 4-year period.[6] A prospective study from Japan showed that the 5-year cumulative incidence of BRI is 2.2% in patients with MMC-augmented trabeculectomy.[8] We did not find an association of BRI with either the concentration or time of MMC applied intraoperatively. It is speculated that when the dosage of MMC is adjusted according to preoperative assessment of the risk of surgical failure caused by postoperative fibrovascular proliferation reaction, the risk of MMC-related complications could be minimised. This may explain, at least in part, why the incidence of BRI in MMC augmented trabeculectomy decreased when surgeons become more familiar with the potential complications of MMC and carefully adjust its concentration used in trabeculectomy.[3–5]

Table 3 Comparisons between cases with blebitis and cases with endophthalmitis

Characteristics	Total BRI n=24	Blebitis n=18	Endophthalmitis n=6	P value
Age at infection ≥60 years, n (%)	12 (50.0)	7 (38.9)	5 (83.3)	0.155
Sex (male %), n (%)	18 (75.0)	15 (83.3)	3 (50.0)	0.139
Best corrected VA, median (IQR)				
The last visit before BRI	0.46 (0.17–1.00)	0.46 (0.22–1.08)	0.43 (0.05–1.10)	0.547
VA at BRI presentation	1.26 (0.33–2.20)	0.55 (0.28–1.90)	2.10 (1.87–2.40)	0.011
One year after BRI	1.00 (0.24–1.39)	0.35 (0.97–1.13)	1.00 (1.00–2.78)	0.030
VA change 1 year after BRI (range)	0.00 (−0.07 to 0.38)	0.00 (−0.10 to 0.02)	0.90 (0.38–1.30)	0.001
IOP (mm Hg), median (IQR)				
Before BRI	12.0 (10.0–14.0)	12.5 (9.8–15.5)	11.0 (9.8–12.5)	0.402
At BRI presentation	11.0 (9.0–17.0)	11.0 (9.0–13.2)	14.5 (7.0–22.0)	0.763
One year after BRI	13.0 (9.3–15.0)	13.0 (9.5–15.0)	14.0 (9.0–20.0)	0.524
Glaucoma medication, n, mean (range)				
Before BRI	0.6 (0.0–3.0)	0.7 (0.0–3.0)	0.3 (0.0–2.0)	0.380
One year after BRI	1.3 (0.0–4.0)	1.2 (0.00–4.0)	1.5 (0.00–4.0)	0.573
High myopia, n (%)	9 (37.5)	9 (50.0)	0 (0.0)	0.052
Repeat trabeculectomy*, n (%)	8 (33.3)	7 (38.9)	1 (16.7)	0.621
Wound manipulation, n (%)				0.670
No wound manipulation	9 (37.5)	6 (33.3)	3 (50.0)	
For IOP control	6 (25.0)	4 (22.2)	2 (33.3)	
Bleb at risk	8 (33.3)	7 (38.9)	1 (16.7)	
Hypotony, bleb leak	1 (4.2)	1 (5.6)	0 (0.0)	
Others	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperlipidaemia, n (%)	7 (29.2)	3 (16.7)	4 (66.7)	0.038

P value is calculated to compare patients with blebitis and with endophthalmitis.
*Repeat trabeculectomy is defined as subsequent trabeculectomy performed before the event of BRI.
BRI, bleb-related infection; IOP, intraocular pressure; VA, visual acuity.

Studies on the effect of high myopia on the BRI risk are lacking. As myopia is a risk factor of glaucoma and global myopia has become an important issue, especially in East Asia,[16] this study result raised attention to surgeons who will encounter more myopic and high myopic patients with glaucoma in the future. Eyes with high myopia are characterised by thin sclera, low scleral rigidity and decreased retinal and choroidal blood perfusion.[17 18] Reduced resistance to bleb infection in eyes with high myopia might be attributable to the thin partial-thickness scleral flap created in trabeculectomy and effects of MMC on the tissue.[19] Further studies are needed to determine the characteristics of high myopia that affect the innate protective mechanism of the eyes after MMC-augmented trabeculectomy. Because myopia is a risk factor for glaucoma[20 21] and the prevalence of myopia is increasing globally,[16] the issue of lifelong risk of BRI in glaucomatous eyes with high myopia after trabeculectomy warrants further attention.

A univariate analysis revealed that younger age was a significant risk factor for BRI; however, this was not indicated in the multivariate analysis. Studies have shown controversial results on young age as a risk factor for BRI.[7 8 22 23] In studies that have shown younger age as a risk factor for BRI, wound manipulation was not considered, unlike in this study. Vigorous wound healing activity in young patients often leads to trabeculectomy failure months to years after surgery, which requires wound manipulation to regain the filtration function, including repeated MMC application.[7 24–28] Wound manipulation has been found to increase risk of BRI in previous studies.[27 28] Exposure to MMC alter the thickness, cellularity, vascularity and immune response of the conjunctiva and tenon tissue, making it vulnerable to bacterial invasion.[29] Another study has shown young patients tend to form a more localised bleb with less vascularity after trabeculectomy, which may heal poorly during minor trauma and be more vulnerable to infection.[30] Accordingly, we believe that the age-related risk of BRI is associated with vigorous wound healing, which either compromises the filtration function, requiring subsequent MMC-augmented transconjunctival revision or yields localised thin blebs due to the formation of fibrotic ring around the blebs in younger patients.[27 28] We further conducted an analysis of the relationship between age and wound manipulation and found that those who were younger than 60 years old were more likely to have wound manipulations than their elder counterparts ($p<0.001$). This result supports our hypothesis proposed above. Our findings suggest that eyes with thin cystic blebs without leakage are at a high risk of BRI (table 2). We tended to perform transconjunctival revision with a needle or bleb knife to relieve the ring of steel to facilitate posterior aqueous drainage in eyes with thin cystic blebs without leak even when the IOP was well controlled, expecting to release the intrableb tension to avoid further thinning. However, this study findings suggest that this approach may not effectively protect the eye from the risk of BRI in the future. A better approach to reduce BRI risk in this scenario may be excision of the avascular cystic tissue with advancement of conjunctiva–tenons capsule flap or application of amnion membrane patch graft on top of the cystic bleb in cases lacking conjunctiva luxury, in addition to relieve the ring of fibrovascular tissue.[14 31]

It is unexpected that hyperlipidaemia, but not diabetes, was a systemic risk factor associated with BRI. We propose that this may

be related to the improvement in care quality for patients with diabetes in Taiwan, so diabetic associated infection may decrease accordingly.[32] Although Lehmann *et al* reported diabetes to be a risk factor for BRI, they did not consider systemic diseases other than diabetes in their analyses.[29] In addition, we propose that impaired innate immune response in hyperlipidaemia, rather than diabetes, might have led to the BRI risk.[33] Another possible explanation is that hyperlipidaemia can cause vascular endothelium dysfunction, leading to poor vascularity around the bleb.[34 35] Blebs with compromised vascularity are vulnerable to microbial infestation when encountered by microtrauma. Further studies are needed to clarify the association between hyperlipidaemia and BRI risk.

Our study has several limitations. First, all surgeries were performed at a single medical centre in Taiwan, and the ethnic and geographic homogeneity of our patients could limit the extrapolation of our findings. Second, many patients were lost to follow-up over a long span of 28 years, which might bias our study results. However, we believe almost all cases of BRI were included in this study due to easy accessibility to medical centre and convenience in transportation in Taiwan. Patients do not need any referral sheet from local clinics or hospitals to reach medical help in a tertiary medical centre. Even if doctors in local clinics or hospitals are alert enough to detect cases of early, mild BRI, they usually ask patients to revisit the hospitals where surgery was performed as soon as possible out of the concern that the medications they prescribe may not be effective to control the infection and doctors in medical centre have more experience in treating patients subsequently in order to prevent another episode of BRI. Third, patients were deemed to have systemic comorbidity based on patient's self-report or the information of medications patients were taking according to patients' national health insurance ID card. We acknowledge that treatment protocol of many systemic diseases is changing over the whole study period, but due to the retrospective nature of this study, we could only show the status when patients received primary trabeculectomy. Even if there was underdiagnosis, the case number of underdiagnosis might be similar across different systemic diseases, thus not significantly affecting our study findings. In addition, we did not record the bleb morphology because it had been changing over the years and different doctors might not record it in a standardised way. Nevertheless, wound manipulation was performed for bleb at risk or leaking bleb, indicating that doctors had paid attention to bleb status during the follow-up period.

In summary, our study revealed that the cumulative incidence of BRI is 1.86 per 1000 person-year after MMC-augmented primary trabeculectomy in a cohort of 1663 eyes. Wound manipulation with transconjunctival revision using a needle or knife which was supplemented with MMC was associated with BRI, as reported in previous studies. In addition, we are the first to report that patients with high myopia and hyperlipidaemia are also at BRI risk. Because the prevalence of hyperlipidaemia and myopia are increasing in many parts of the world and myopia is a known risk factor for glaucoma, the new findings warrant the attention of the ophthalmology society. Patients with a history of trabeculectomy should be informed regarding the significance of ocular pain associated with red eye for timely identification and management of BRI.

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