Original Article

Factors related to filtration-bleb morphology after Ex-PRESS® surgery

Naoki Tojo, Atsushi Hayashi, Mitsuya Otsuka

Purpose: We investigated the factors influencing the morphology of filtration blebs after Ex-PRESS® surgery. We analyzed the thickness of the bleb wall and the height and the volume of blebs. **Methods:** This was a retrospective non-randomized study. After excluding patients who had undergone an additional glaucoma surgery, we analyzed the cases of 145 consecutive patients (180 eyes) who underwent trabeculectomy with Ex-PRESS® for the first time at Toyama University Hospital and were followed for >1 year. We used anterior segment optical coherence tomography to analyze the morphology of the blebs after Ex-PRESS surgery. We also examined potential influencing factors including age, central corneal thickness, type of glaucoma (primary open-angle glaucoma [POAG] or pseudo-exfoliation glaucoma [PEXG]), preoperative intraocular pressure (IOP), postoperative IOP, history of trabeculotomy, and operation method: Ex-PRESS surgery only, or simultaneous cataract surgery. **Results:** Ex-PRESS surgeries significantly decreased the IOP from 24.5 ± 8.8 mmHg to 11.1 ± 3.4 mmHg after 1 year ($P < 0.001$). The cases with higher blebs, larger volume of blebs, and thinner bleb wall had better surgical outcomes. **Conclusion:** Advanced age, higher postoperative IOP, PEXG, and simultaneous cataract surgeries were found to decrease the volume and height of blebs. Younger age, higher postoperative IOP, POAG, and simultaneous cataract surgeries were found to thicken the wall of blebs. Among the younger patients, there were many cases in which surgery was unsuccessful in spite the large volume of blebs. The reason for this may be that the wall of the bleb is thick.

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Trabeculectomy is the most common glaucoma surgery. In a trabeculectomy, a bleb is formed in the sub-tenon space to receive the outflow of aqueous humor, thereby lowering the intraocular pressure (IOP). The morphology of the bleb after trabeculectomy is an important clinical parameter and has been analyzed in numerous studies that have revealed, for example, that the wall thickness, height, and volume of the bleb correlate with the IOP.[1-5]

The main causes of failure blebs are the natural repair mechanisms of the eye leading to excessive wound healing in the surgical area and the episcleral fibrosis causing decreased flow and resulting in decreasing bleb or flattening of the bleb.[6] It is important to maintain a large bleb for a long period to maintain a low IOP value. Thus, it is useful to measure the volume of the bleb periodically. The Indiana Bleb Appearance Grading Scale is widely used in classifications of the morphology of filtration bleb.[7] This classification is a simple and easy to test as it can be inspected with a slit lamp. However, even among trabeculectomies with a large bleb, there are cases with high IOP, such as those with an encapsulated bleb. It is relatively difficult to determine the precise morphology of a bleb with a slit-lamp examination, which has been used clinically for this purpose. The more recently developed anterior segment optical coherence tomography (AS-OCT) approach has made it easier to measure the morphology of blebs.[8,9]

There are several surgical methods used to make blebs, as a conventional trabeculectomy: a trabeculectomy with a mini-shunt called the Ex-PRESS® (Alcon Laboratories, Fort Worth, TX), ologen® (Aeon Astron Europe B. V., Leiden, the Netherlands), etc. Many studies have compared conventional trabeculectomy and trabeculectomy with Ex-PRESS.[10-13] The Ex-PRESS surgery has produced outcomes that are similar to those obtained with a conventional trabeculectomy, with fewer early postoperative complications because of its low rate of over-filtration. Other advantages of the Ex-PRESS surgery are that the lumen of the device is standardized constantly, and the outflow is predictable. Although some studies have discussed the size of blebs after a conventional trabeculectomy, there have been few reports about the size of blebs after Ex-PRESS surgery.[1-5] Herein, we measured the thickness of the bleb wall and the height and the volume of blebs of patients who underwent an Ex-PRESS trabeculectomy, and we investigated the factors influencing the morphology of the blebs and their correlation with surgical results.

Methods

Patients

This was a retrospective, non-randomized observational study. We analyzed the cases of 145 consecutive patients (180 eyes)

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who underwent trabeculectomy with Ex-PRESS® for the first time at Toyama University Hospital and were followed for >1 year. Because Ex-PRESS surgery is contraindicated for use in patients with uveitis or primary angle closure glaucoma, we performed trabeculectomy with the Ex-PRESS only for patients with primary open angle glaucoma (POAG) or pseudo-exfoliation glaucoma (PEXG). There were 35 patients who underwent trabeculectomy with the Ex-PRESS in both eyes, and in these cases, we used unilateral data of the eye that was operated earlier.

All subjects were recruited during the period from January 2013 to July 2017. All patients underwent a comprehensive ophthalmic examination including refraction, Goldmann gonioscopy, Goldmann applanation tonometry (GAT), a fundus examination, automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA), and the measurement of the central corneal thickness (CCT) and anterior chamber depth with AS-OCT (CASIA SS-1000; Tomey, Nagoya, Japan). Two glaucoma specialists (N.T. and A.H.) diagnosed all of the cases of glaucoma. The preoperative (baseline) IOP was the mean of the IOPs recorded at three of the patient's visits while on preoperative treatment. The IOP was measured using GAT.

The patients had already used tolerated glaucoma medications but required further treatment to lower their IOP because of the progression of their visual field disorder. The research protocol was approved by the Institutional Review Board of the University of Toyama, and the procedures used conformed to the tenets of the Declaration of Helsinki. After the nature and possible consequences of the study were explained to the patients, written informed consent was obtained from all individual participants included in the study.

Surgical techniques

All patients were operated on by one surgeon (N.T.). The surgeon in this study has abundant experiences of conventional trabeculectomy. From patients who underwent Ex-PRESS surgery for the first time, all patients were included in this study. Retrobulbar anesthesia was administered. A standard fornix-based conjunctival incision was made to gain exposure to the scleral bed adjacent to the limbus. A single 3.5-mm^2 square scleral flap was created. Mitomycin C (MMC) solution (0.04 mg/ml) was applied below conjunctiva and below scleral flap for 4 min. At this point, the eye was a completely enclosed space, and thus, the MMC solution could not flow into the anterior chamber. The treated area was then irrigated with approximately 100 ml of balanced salt solution. If the patient needed simultaneous cataract surgery, the cataract surgery was performed at this time. Phacoemulsification was performed with a WhiteStar Signature system (Abbott Medical Optics, Santa Ana, CA); IOL was implanted from the clear temporal cornea.

Regarding the surgical indications for cataract surgery, this was a retrospective study, no clear criteria were established as visual acuity or Emery grades or age, and cataract surgery was performed according to the judgment of the operator. The scleral flap was lifted, and a 25-ga. needle was horizontally inserted into the anterior chamber at the surgical limbus to create a path for the Ex-PRESS (model P50); the 25-ga. needle was inserted into the anterior chamber from the sclera-cornea transition zone parallel with the iris. The Ex-PRESS shunt was then inserted into the anterior chamber.

The scleral flap was sutured using 10-0 nylon, whereas the tension on the sutures was adjusted to maintain the anterior chamber depth with a slow flow of aqueous humor around the margins of the scleral flap. The conjunctiva was meticulously closed with 10-0 nylon sutures. We confirmed that there was no leakage from the blebs.

Postoperative medication

The postoperative treatments consisted of topical steroids, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs). The antibiotics were reduced over the 4 weeks following the interventions. The steroid and NSAIDs were reduced over a 12-week period after the interventions. Anti-glaucoma medications were added at the discretion of the physicians. We counted a compounding agent as two medications.

Evaluation of the volume of blebs

At 1 year after each trabeculectomy with the Ex-PRESS, filtering bleb images (12 × 12 mm^2) were acquired using AS-OCT. We used the CASIA bleb assessment software package (ver. 4.0L; Tomey, Nagoya, Japan) to analyze the morphology of each bleb.

The volume of blebs was measured automatically. In principle, for the measurement of the volume of a bleb, AS-OCT measured the size of the hypo-reflective area with a C-scan (X-Y cross-section). In addition, while changing the position of the Z-axis, we measured the hypo-reflective area of each section and calculated the volume of the bleb by integrating each hypo-reflective area. The thickness of 1 slice was approximately 10 μm. We did not perform any additional manual measurements for the volume of blebs [Fig. 1a].

We measured the thickness of the bleb wall and the height of the bleb manually. We defined the height of bleb as the maximum distance between the sclera and the inside of the bleb wall. We defined the thickness of the bleb wall as it was measured at almost the center of the bleb [Fig. 1b]. Because these measurement methods may have poor reproducibility, the morphology of each bleb was measured twice by two researchers, and the results of these measurements were used to check the accuracy of the automatic measurement. We used the mean value of the two measurements. For the cases with additional glaucoma surgery, we used the data obtained immediately before additional glaucoma surgery.

We conducted a statistical analysis to determine whether various factors influenced the size or retention rate of the blebs. These factors were the patient's age, CCT, glaucoma

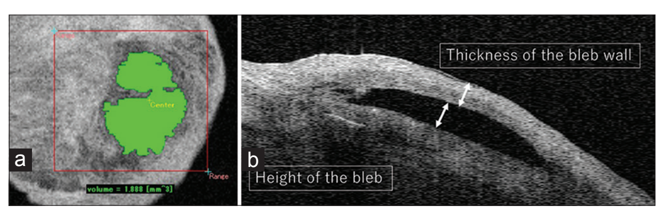

Figure 1: (a) Representative result of measurement of the volume of a bleb by anterior segment optical coherence tomography (AS-OCT). (b) Representative result of measurement of the height of a bleb and the thickness of a bleb's wall with AS-OCT

type (POAG or PEXG), history of previous glaucoma surgery, preoperative IOP, postoperative IOP, history of trabeculotomy, and operation method: Ex-PRESS surgery alone (Single surgery) or phacoemulsification + intraocular lens implantation and Ex-PRESS surgery simultaneously (Triple surgery)).

Definition of success

We used two main criteria of successful treatment. Success according to Criterion A was defined as postoperative IOP ≤21 mmHg and a ≥20% reduction from the baseline on two consecutive visits after the first postoperative month. Success according to Criterion B was defined as postoperative IOP ≤15 mmHg and a ≥20% reduction from the baseline on two consecutive visits after the first postoperative month. Cases were considered treatment failures if neither of the success criteria was met at two consecutive visits after the first postoperative month. Eyes requiring additional glaucoma surgery and those that developed phthisis or showed a loss of light perception were classified as failures. Needling was not included in additional surgery.

Statistical analysis

A Wilcoxon signed-rank test was used to compare IOP levels and the numbers of glaucoma medications. A Kaplan-Meier survival analysis and log-rank tests were used for the comparison of the success rate. Influencing factors for the morphology of blebs were identified using a canonical correlation analysis and multiple regression analysis. We determined Pearson's correlation coefficients. All of the statistical analyses were performed with JMP Pro 11 software (SAS, Cary, NC). Significance was defined as P values <0.05.

Results

Ophthalmic data

The characteristics of the patients are summarized in Table 1. We analyzed the cases of 145 patients: 77 males and 68 females. The mean (± standard deviation) values for all 145 patients were as follows: age at the time of surgery, 70.1 ± 10.5 years; CCT, 527 ± 34 μm; follow-up period, 33.4 ± 10.2 months; number of preoperative glaucoma medications, 4.0 ± 0.9; and preoperative IOP, 24.5 ± 8.8 mmHg. One hundred eyes underwent trabeculectomy with the Ex-PRESS alone: the lens was preserved as phakia in only two cases, and the other 98 of the 100 eyes had already undergone cataract surgery. The other 45 eyes were phakic and underwent cataract surgery and trabeculectomy with Ex-PRESS simultaneously. Thirty patients had previously undergone trabeculotomy (including Trabectome® or canaloplasty). We classified the subtypes of glaucoma as POAG (n = 70 patients) and PEXG (n = 75); there were no other glaucoma subtypes. In our study, there were no cases with endophthalmitis or expulsive hemorrhage. There were two cases that occurred bullous keratopathy because of positional abnormality of Ex-PRESS. There were two cases of increased IOP owing to occlusion of Ex-PRESS. Both cases could release occlusion with laser treatment.

Postoperative IOP and success rate

We performed a Kaplan-Meier analysis to determine the success rates of the 145 eyes for both Criterion A and Criterion B [Fig. 2]. Table 2 summarizes the postoperative IOP and medication data of the Ex-PRESS surgeries. The reasons for treatment failure with Criterion B were as follows: Additional glaucoma surgery was required (18 eyes); postoperative IOP reduction from the baseline on two consecutive visits ≥ 20% (2 eyes); and loss of light sensation (2 eyes).

Table 1:Characteristics of study subjects

Items	Mean±SD
Age (years old)	70.1±10.5
Gender (male/female)	77/68
CCT (μmCT)	527±34
Pre IOP (mmHg)	24.5±8.8
Pre-medications	4.0±0.9
Follow-up periods (months)	33.4±10.2
POAG/PEXG	70 eyes/75 eyes
History of TLO	30 eyes (20.7%)

CCT=Central corneal thickness, IOP=Intraocular pressure, POAG=Primary open angle glaucoma, PEXG=Pseudo-exfoliation glaucoma, TLO=Trabeculotomy (including Trabectome® or canaloplasty)

Table 2: Postoperative IOP and medications

Periods (n)	IOP (mmHg)	Medications
Preoperative (145)	24.5±8.8	4.0±0.9
Postoperative 1 year (134)	11.1±3.4	1.5±1.6
Postoperative 2 years (86)	11.5±3.7	2.0±1.7
Postoperative 3 years (41)	11.4±4.7	2.5±1.7
Postoperative 4 years (22)	11.0±3.7	2.1±1.7
Postoperative 5 years (5)	12.4±3.2	3.8±0.5

IOP=Intraocular pressure

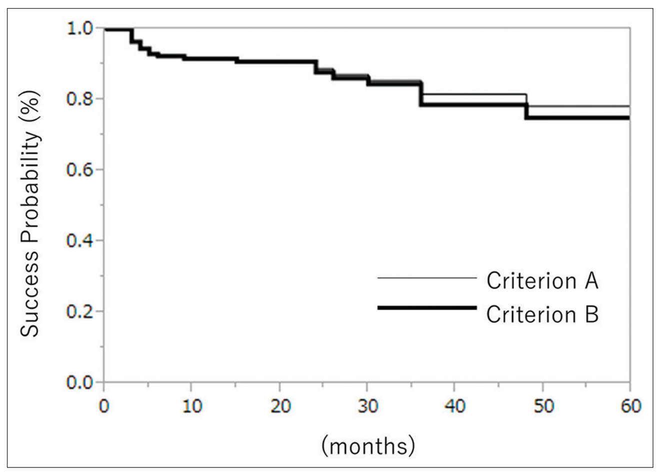

Figure 2: Kaplan-Meier survival curves for Criterion A (postoperative IOP ≤21 mmHg and ≥20% reduction from the baseline) and Criterion B (postoperative IOP ≤15 mmHg and ≥20% reduction from the baseline)

Morphology of the blebs and influencing factors

There was no case in which we could not analyze the volume of a bleb with AS-OCT. At 1 year after surgery, the mean height of the bleb, the thickness of the bleb wall, and the volume of the bleb were 1.25 ± 0.43 mm, 0.56 ± 0.23 mm, and 4.45 ± 6.08 mm^3, respectively [Table 3].

Fig. 3 shows the correlation between 4 factors (age, pre-operative IOP, CCT, and postoperative IOP) and the height of blebs at 1 year post-surgery. Younger age and

Table 3: Comparison of the bleb volume after 1 year with influence factors (the mean value±standard deviation)

	(eyes)	Height of bleb (mm)		Thickness of bleb wall (mm)		Volume of bleb (mm^3)	
		Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*
Total	(145)	1.25±0.43		0.56±0.23		4.45±6.08	
Gender	Male (77)	1.25±0.41	0.87	0.57±0.21	0.679	4.51±5.81	0.899
	Female (68)	1.24±0.46		0.55±0.25		4.38±6.33	
Subtype	POAG (70)	1.34±0.46	**0.0125**	0.62±0.26	**0.0011**	5.59±7.31	**0.0231**
	PEXG (75)	1.16±0.38		0.49±0.18		3.29±4.22	
Operation	Single (100)	1.30±0.43	**0.0421**	0.52±0.21	**0.0041**	5.12±6.80	**0.0481**
	Triple (45)	1.14±0.40		0.64±0.25		2.97±3.71	
History of TLO	A (30)	1.18±0.41	0.327	0.56±0.24	0.735	3.83±3.58	0.533
	A/N (115)	1.27±0.44		0.55±0.20		4.61±6.58	
Success A	Success (125)	1.28±0.44	**0.0093**	0.54±0.23	**0.0122**	4.92±6.35	**0.0185**
	Fail (20)	1.01±0.23		0.68±0.17		1.47±2.65	
Success B	Success (123)	1.28±0.44	**0.0389**	0.54±0.24	**0.0139**	4.73±5.89	0.196
	Fail (22)	1.07±0.29		0.67±0.17		2.91±7.03	

POAG=Primary open angle glaucoma, PEXG=Pseudo-exfoliation glaucoma, Single=Trabeculectomy with Ex-PRESS® alone, Triple=Trabeculectomy with Ex-PRESS®, phacoemulsification, and intraocular lens, TLO=Trabeculotomy, *P*<0.05 Bold

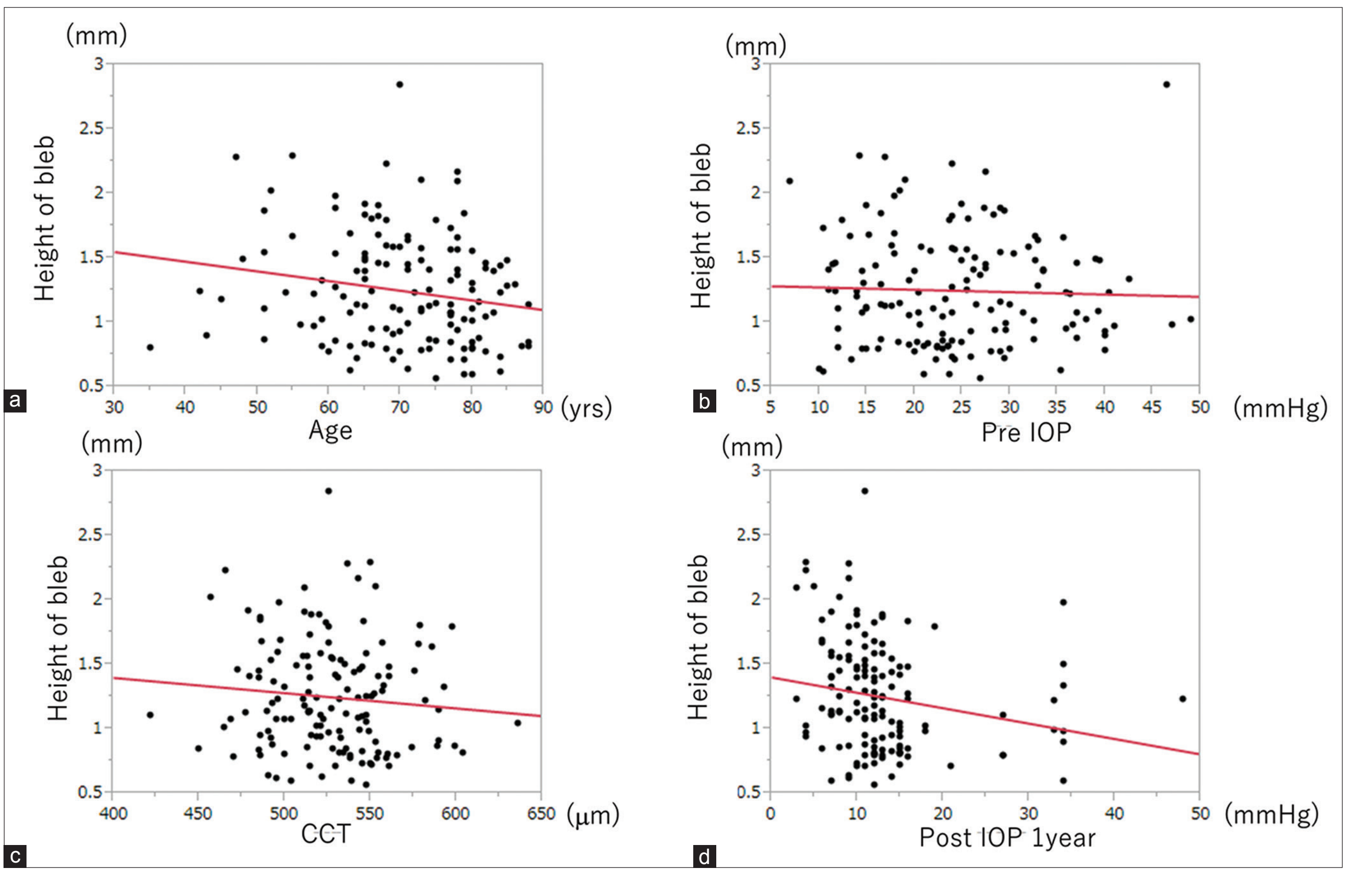

Figure 3: (a) The correlation between patient age and the height of blebs at 1 year post-surgery. Younger patients had significantly higher blebs (*P* = 0.0185). (b) The correlation between the preoperative IOP and the height of blebs. There was no significant correlation (*P* = 0.822). (c) The non-significant correlation between the CCT and the height of blebs (*P* = 0.148). (d) The correlation between postoperative IOP and the height of blebs. Lower the postoperative IOP was, significantly higher the blebs were (*P* < 0.001)

low postoperative IOP patients had significantly higher blebs (*P* = 0.0185 and *P* < 0.0001).The factors that significantly influenced the height of bleb were type of glaucoma (*P* = 0.0125), method of surgery (*P* = 0.0421), and the success rate (Criteria A and B) (*P* = 0.0093, *P* = 0.0389) [Table 3].

Fig. 4 shows the correlations between 4 factors and the thickness of the bleb walls at 1 year post-surgery. Younger age and high postoperative IOP patients had significantly thicker bleb walls (*P* < 0.0001 and *P* < 0.0401).The factors that significantly influenced the thickness of the bleb wall were type

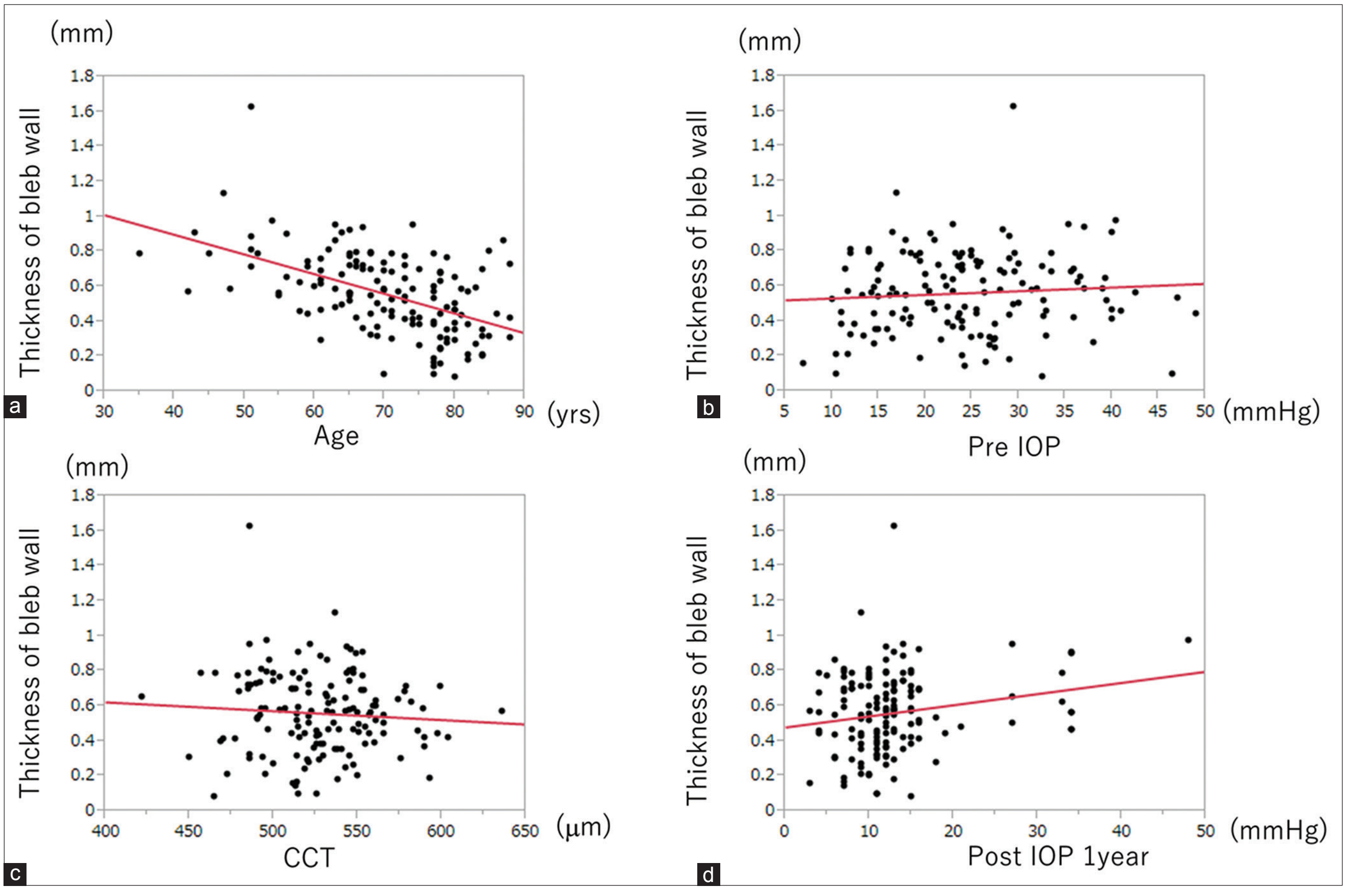

Figure 4: (a) The correlation between age and the thickness of the bleb wall at 1 year post-surgery. Younger patients had significantly higher blebs ($P < 0.001$). (b) The correlation between the preoperative IOP and the thickness of bleb wall at 1 year post-surgery. There was no significant correlation ($P = 0.732$). (c) The non-significant correlation between the CCT and the thickness of bleb wall at 1 year post-surgery ($P = 0.375$). (d) The correlation between postoperative IOP and the thickness of the bleb wall at 1 year post-surgery. Lower the postoperative IOP was, significantly higher the blebs were ($P = 0.040$)

of glaucoma ($P = 0.0011$), method of surgery ($P = 0.0041$), and the success rate (Criteria A and B) ($P = 0.0122$, $P = 0.0139$) [Table 3].

Fig. 5 shows the correlations between 4 factors and the volume of the blebs at 1 year post-surgery. Younger age and high postoperative IOP patients had significantly larger bleb ($P < 0.0484$ and $P < 0.0002$).The factors that significantly influenced the volume of the blebs were type of glaucoma ($P = 0.0231$), method of surgery ($P = 0.00481$), and the success rate (Criteria A) ($P = 0.0185$) [Table 3].

To summarize Table 3, compared to the POAG patients, the PEXG patients had low, small blebs, and thin bleb walls. Compared to the Single surgery, the Triple surgery resulted in low, small blebs, and thick bleb walls. Patients with unsuccessful surgery had low, small blebs and thick bleb walls. Table 4 summarizes Figs. 3-5 and shows the correlation with morphology of blebs and the correlation coefficient. Younger patients had significantly larger and higher blebs and thicker bleb walls. The blebs with high postoperative IOP were small and low, with a thick wall.

The factors influencing the surgical outcomes

We examined whether the morphology of blebs affected the surgical outcomes. Fig. 6a shows the Kaplan-Meier survival plots comparing younger patients (≤70 years old) and older patients (>70 years old) with Criterion B. The elderly patients achieved significantly better surgical outcomes ($P = 0.0150$). Fig. 6b shows the Kaplan-Meier survival plots comparing the POAG and PEXG groups. There was no significant difference between the two groups with Criterion B ($P = 0.801$). Fig. 6c provides the Kaplan-Meier survival plots comparing the Triple surgery and Single surgery groups; there was no significant difference between the two groups with Criterion B ($P = 0.653$). The Kaplan-Meier survival plots comparing the patients with and without a history of trabeculotomy are given in Fig. 6d: there was no significant difference between the two groups with Criteria B ($P = 0.844$).

Discussion

Trabeculectomy with the Ex-PRESS significantly reduced the IOP from 24.5 ± 8.8 mmHg to 11.1 ± 3.4 mmHg at 1 year post-surgery [Table 2]. The success rate with Criterion B was 91.7% after 1 year. These surgical results are comparable to those of conventional trabeculectomy [Fig. 2].[1-5] Regarding the morphology of the blebs, larger bleb volume, greater bleb height, and thinner bleb wall were factors for low IOP. These results are nearly the same as those in previous reports about conventional trabeculectomy. Good *et al*. reported that the comparison of morphologic blebs between Ex-PRESS surgery and conventional trabeculectomy with Moorfields Bleb

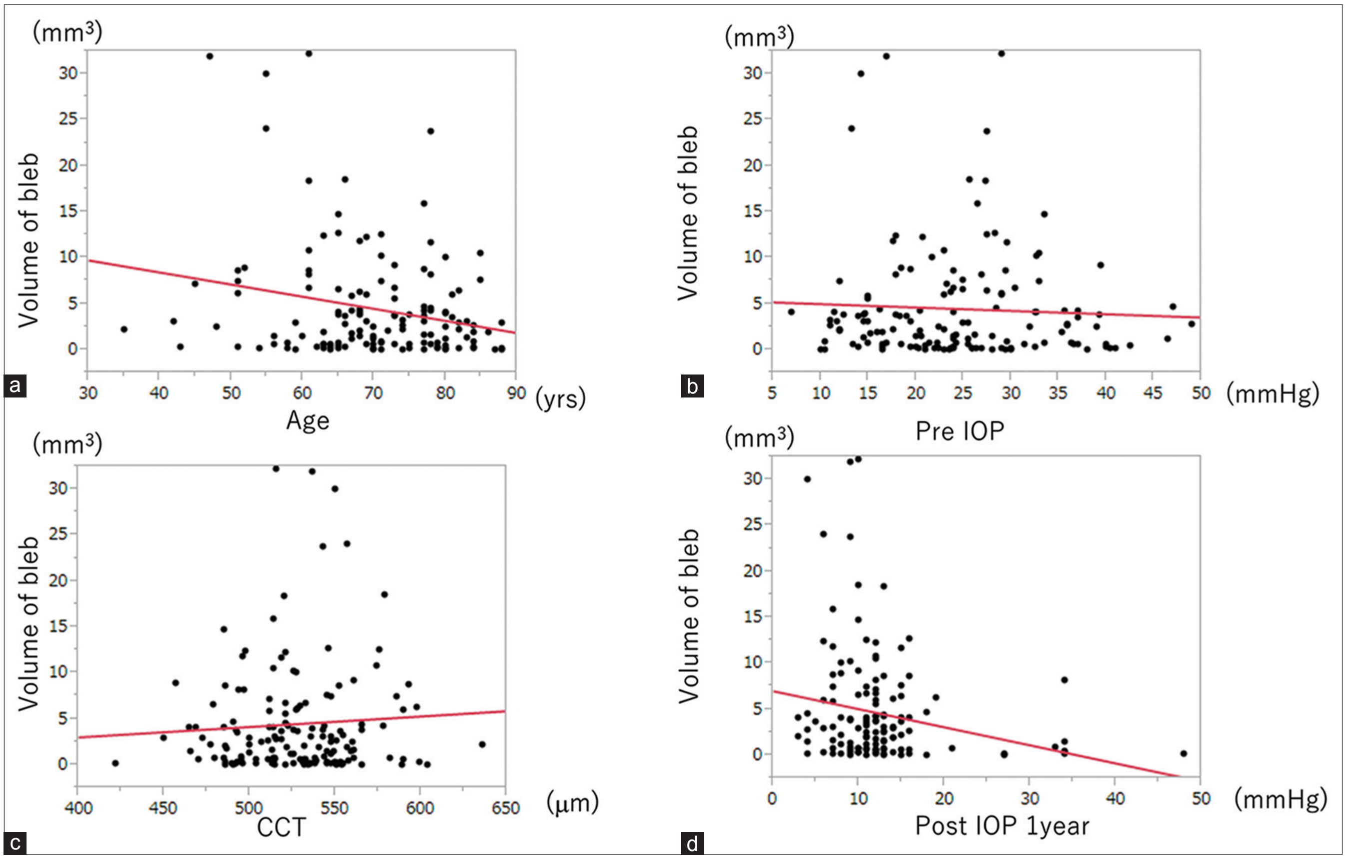

Figure 5: (a) The correlation between patient age and the bleb volume at 1 year post-surgery. The younger patients had significantly larger blebs (*P* = 0.0484). (b) The correlation between the preoperative IOP and the bleb volume at 1 year post-surgery; n.s. at *P* = 0.701. (c) The non-significant correlation between the CCT and the bleb volume at 1 year post-surgery; *P* = 0.949. (d) The correlation between postoperative IOP and the bleb volume at 1 year post-surgery. Lower the postoperative IOP was, significantly higher the blebs were (*P* = 0.0002)

Table 4: Correlation with the morphology of the blebs

	Height of bleb		Thickness of bleb wall		Volume of bleb	
	P	Correlation coefficient (*P*)	*P*	Correlation coefficient (*P*)	*P*	Correlation coefficient (*P*)
Age (years old)	**0.0274**	0.1955 (***P*=0.0185**)	**<0.001**	0.4936 (***P*<0.001**)	**0.0058**	0.1576 (***P*=0.0484**)
CCT (mCT	0.257	0.1206 (*P*=0.1483)	0.372	0.0742 (*P*=0.3749)	0.411	0.0054 (*P*=0.9490)
Pre-IOP (mmHg)	0.651	0.0189 (*P*=0.8219)	0.338	0.0287 (*P*=0.732)	0.523	0.0322 (*P*=0.7008)
Post-IOP 1 year (mmHg)	**0.0170**	0.348 (***P*<0.001**)	**0.0179**	0.1707 (***P*=0.0401**)	**0.0052**	0.3021 (***P*=0.0002**)

Correlation coefficient=Spearman correlation coefficient (ro, CCT=Central corneal thickness, Pre-IOP=Preoperative intraocular pressure, Post-IOP=Postoperative intraocular pressure, (Bold letters are significant)

Grading System.[14] Although they reported that the bleb after Ex-PRESS was less vascular and lower height but more diffuse area than trabeculectomy, these differences did not exist after 2 years, and the bleb morphologic features also were similar. Matusmoto *et al.* reported that wider bleb was a factor for long-term IOP control.[3] Narita *et al.* observed that high blebs had better surgical results than conventional trabeculectomy.[2] According to a study by Tominaga *et al.*, the height and extent of the total bleb and the internal cavity were not correlated with IOP control.[15] The higher and larger blebs and the thinner bleb walls were significantly better surgical results. In cases with postoperative IOP ≤15 mmHg (Criteria B), there was no a significant difference in the volume of the blebs between success and failure groups (*P* = 0.196). This might suggest that reducing postoperative IOP less than 15 mmHg require not only large blebs but also high blebs and thin bleb walls.

Several research groups have indicated that the low reflection area of the bleb wall after conventional trabeculectomy during the early postoperative period might be associated with lower IOP.[1-5,15] In the present study, we investigated the morphology of blebs at 1 year after Ex-PRESS surgery rather than during the early postoperative period. There was no case in which a low-reflex area was observed in the bleb wall at 1 year after Ex-PRESS surgery. The reason for this might be on basis of the fact that the amount of aqueous outflow in an Ex-PRESS surgery is smaller than that in a conventional trabeculectomy. There are no reports about morphological changes of blebs after Ex-PRESS surgery. The thinner the bleb, the lower the

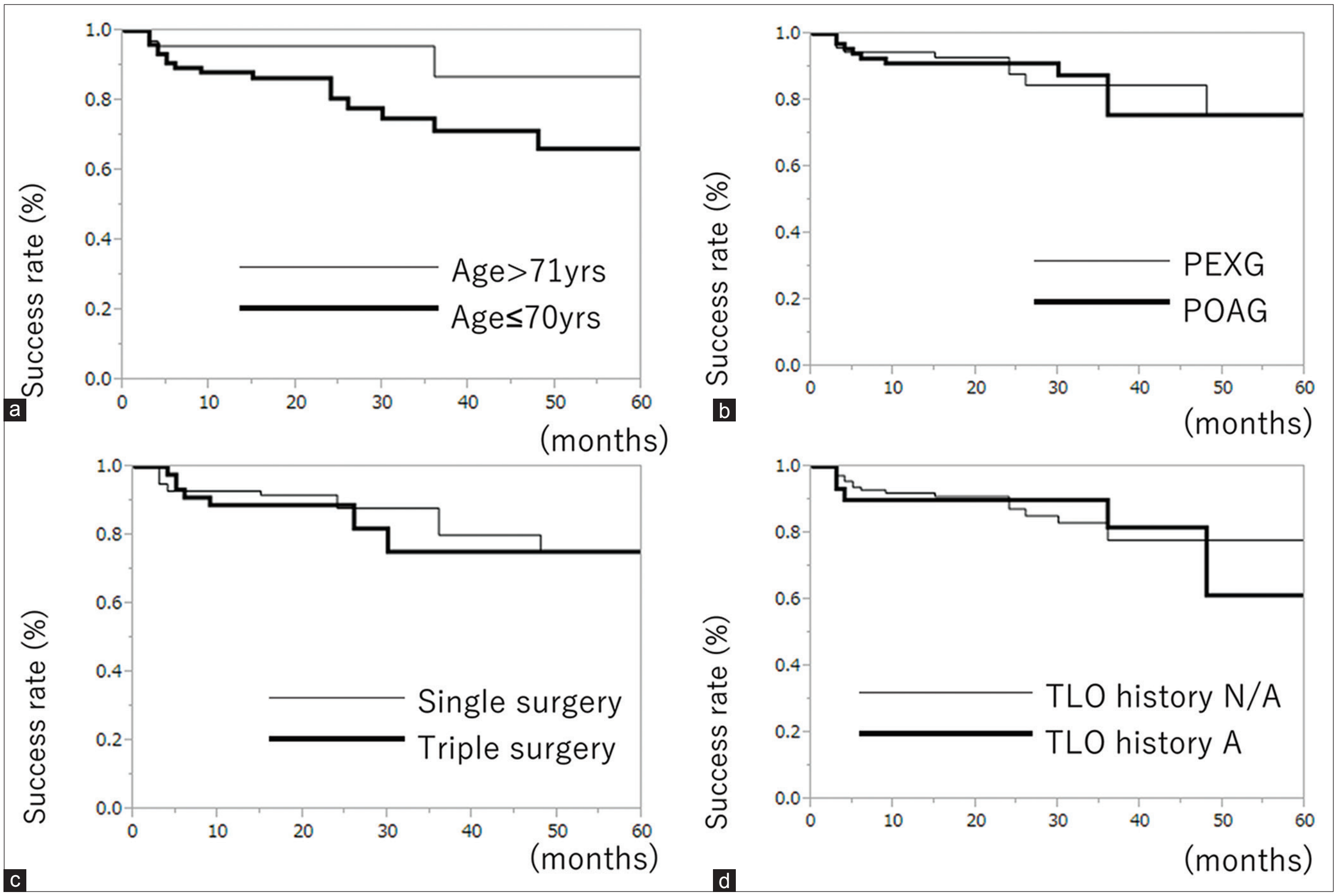

Figure 6: (a) Kaplan-Meier survival plots comparing younger patients ($\leq$70 years old; bold line) and older patients (>70 years old; normal line) with Criterion B. The older patients had significantly better surgical results ($P = 0.0150$). (b) Comparing POAG (bold line) and PEXG (normal line) case with Criterion B. There was no significant difference ($P = 0.801$). (c) Comparing Triple surgery (bold line) and Single surgery (normal line) with Criterion B ($P = 0.653$). (d) Comparing the patients with a history of TLO surgery (bold line) and those without a history of TLO surgery (normal line) with Criterion B ($P = 0.844$)

postoperative IOP is. The thinning of a bleb presents a risk of leakage over a long-term follow-up.

There are many reports that trabeculectomy is more unsuccessful for young patients.[16-18] In our study, the younger patients (≤70 years) had significantly lower surgical success rates in spite the fact that their blebs were significantly larger [Fig. 6a]. This indicates that it is not possible to fully explain the surgical outcomes based solely on the volume of the bleb in a given case. Although our younger patients had significantly larger blebs, the walls of the blebs were significantly thicker. This may be why there is a significantly poorer success rate among younger patients. The tenons of young patients are often firmly adhered to the conjunctiva at the conjunctival limbs, and this may be related to the thickening of the bleb wall in these patients. Thus, our results appear to deviate from the previous reports in which younger patients had smaller blebs. Our findings suggest that younger patients are more likely to have encapsulated blebs. This study is a retrospective study, and data of cases with additional surgery has been deleted. Therefore, it may be suggested that successful cases with young patients require a large bleb.

Compared with POAG, the blebs with PEXG were significantly smaller and lower, and the bleb walls were thinner [Table 3].Although the volume of blebs was small in the PEXG group, the surgical results were comparable to those of POAG. We speculate that the reason for this is the thin bleb wall. The PEXG patients were significantly older than the POAG patients (POAG: 66.0 ± 10.9, PEXG: 74.2 ± 8.4 years old) ($P < 0.001$), and this may have affected the surgical outcomes. In our study, it is unclear whether it is influenced by age or glaucoma subtype. We should study age matched.

The eyes with PEXG had significantly smaller blebs than those with POAG [Table 3] ($P = 0.0231$). The reason why the blebs with PEXG become smaller may be owing to inflammation involving the extracellular matrix in the eyes of the patients with PEXG. Browne *et al.* reported that compared to the aqueous humor of POAG patients, the aqueous humor of PEXG patients contained greater levels of a connective tissue growth factor that increases the production of fibrillin-1.[19] The reason why blebs with PEXG have a thinner wall might be because of the greater proportion of elderly patients with PEXG.

Compared to the present Single surgery group, the Triple surgery group had significantly smaller and lower blebs, and the bleb walls were thicker. In addition, the Triple surgery group had significantly more younger patients ($P < 0.001$). To suggest correctly that Triple surgery become poor results, it is desirable to study age matched. Although the Triple surgery group included factors of poor surgical results, the success rate was not significantly different from that of the Single surgery group [Fig. 6c]. Ogata-Iwao *et al.* reported that Triple surgery had worse surgical outcomes than Single surgery.[20] Inoue *et al.* noted that monocyte chemotactic protein-1, which is a prognostic factor for the results of trabeculectomy, increased when cataract surgery was performed.[21,22] In this way, the characteristic cytokines that are increased as a result of cataract surgery may cause smaller blebs in patients undergoing Triple surgery. However, Anton *et al.* reported that the results of trabeculectomy with simultaneously cataract surgery were good and should not be restricted.[23]

Our study has several limitations. The most important was the retrospective, non-comparative design. Because of this study design, it was not possible to evaluate the volume of the blebs in the patients who needed additional glaucoma surgeries. The small number of patients was another limitation; a larger prospective comparative study is needed to fully investigate the bleb volumes.

Conclusion

In conclusion, the presence of a large bleb, high bleb, or thin bleb wall lowered the postoperative IOP. It is difficult to make ideal filtration cells as desired. Further investigations of the morphology of blebs might lead to improvements in surgical outcomes.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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Conflicts of interest

There are no conflicts of interest.

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