Evaluation of Subconjunctival Bleb Function after Trabeculectomy with Mitomycin C using Ultrasound Biomicroscopy

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ABSTRACT

Purpose: To investigate the relationship between filtering bleb function and ultrasound biomicroscopic (UBM) images. Materials and Methods: The study analyzed UBM parameters, including intrableb reflectivity, maximum height of the subconjunctival filtering bleb, the route under the scleral flap, and the presence of intrableb microcysts, in correlation to surgical outcomes. The trabeculectomy blebs were accepted clinically successful when the post-operative IOP was ≤21 mmHg without antiglaucoma medications. Results: A total of 63 eyes of 52 patients were included in the study. The median time between trabeculectomy and the UBM examination was 41 mo (range, 2-188 mo). The surgery was completely successful in 23 eyes, partially successful in 31 eyes, failed in 9 eyes. The presence of cysts inside the bleb was correlated significantly with complete success (p=0.007). The completely visible route under the scleral flap was significantly frequent in cases of complete and partially successful cases than functional failure cases (p<0.001). The median maximal height of the filtering bleb was significantly higher in cases of complete success (1.4, 0.8-3.0 µm) than partial success (0.9, 0.5-2.2 µm) and failed (0.7, 0.4-1.4 µm) subgroup (p<0.001). The high-reflectivity filtering bleb was significantly frequent in cases of functional failure than other groups (p<0.001). Conclusion: Ultrasound biomicroscopy is an useful imaging modality for the functional evaluation of the bleb after trabeculectomy. The presence of visible route under the scleral flap, intrableb cysts, low reflectivity and high bleb height in UBM increase the success of trabeculectomy surgery.

Keywords: Bleb reflectivity, filtering bleb, intrableb cysts, trabeculectomy, ultrasound biomicroscopy

INTRODUCTION

Since 1960, trabeculectomy has been the standard surgical procedure for treating glaucoma.[1] The formation of a filtering bleb, an artificial channel that facilitates the drainage of aqueous humor into the subconjunctival region, is critical for the success and efficacy of trabeculectomy. Adequate aqueous outflow to the bleb and its subsequent absorption are essential for controlling intraocular pressure (IOP) following the surgery.[2] Mitomycin C (MMC) is commonly used during the procedure to modulate wound healing and improve surgical outcomes.[3]

The appearance and functionality of blebs are typically assessed based on subjective clinical evaluations, which consider the presence of subconjunctival microcysts, bleb height and width, and conjunctival vascularization. The morphology of blebs, a crucial indicator of both bleb function and complications, can be described and categorized using various clinical grading systems based on slit-lamp examination.[4] However, these grading systems lack the ability to visualize the internal structure of the bleb. Ultrasound biomicroscopy (UBM) provides high-resolution imaging, enabling precise measurement of bleb thickness and visualization beneath the scleral flap.[5]

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In this study we assessed the UBM characteristics of filtering blebs following trabeculectomy to evaluate whether the ultrasound biomicroscopic images correlate with bleb function.

METHODS

This study was approved by the local ethics committee (Ankara University Faculty of Medicine, Ankara) and was conducted in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all patients prior to surgery.

The subjects in this study were 63 eyes of 52 patients who had trabeculectomy during the period from October 2006 to May 2019. UBM examinations were performed from July 2013 to December 2019. The patients' eye characteristics and demographics are listed in Table 1. The postoperative IOPs before UBM examination were assessed with a Goldmann applanation tonometer in the seated position by the same author (OT)

The IOP was used to determine clinical success. Surgical complete success was defined as an IOP ≤21 mmHg without the use of any medication. Partially successful bleb was defined as an IOP ≤21 mmHg with antiglaucoma medications. Failure cases were defined as an IOP >21 mmHg despite all lines of antiglaucoma medications.

Ultrasound Biomicroscopy Model P40 (Paradigm Medical Industries, Inc., Salt Lake City, UT, U.S.A.) was used in the present study. UBM examinations was performed 2 to 188 months (median 41 mo) after surgery by a single investigator (MBH) who was masked to postoperative IOP and other personal data of the patients. For UBM, the patient was under topical anesthesia in the supine position using an eye cup filled with polyacrylic acid 0.2% (Viscotears

Table 1. *Patient/Eye Characteristics*

Variable	Total	Failed	Partially successful	Complete successful	p-value
Number of patients, *n(%)*	**52 (100)**	**8 (15.4)**	**25 (48.1)**	**19 (36.5)**	
Gender, *n(%)*					
Male	28 (53.8)	6 (75.0)	14 (56.0)	8 (42.1)	0.313*
Female	24 (46.2)	2 (25.0)	11 (44.0)	11 (57.9)	
Age (years)	62 (22-82)	62 (55-82)	64 (23-81)	61 (22-75)	0.369#
Number of eyes, *n(%)*	**63 (100)**	**9 (14.3)**	**31 (49.2)**	**23 (36.5)**	
Period between trabeculectomy and UBM examination (months)	41 (2-188)	28 (3-83)	41 (3-188)	43 (2-123)	0.398#
Preoperative IOP (mmHg)	34 (26-58)	32 (26-46)	35 (27-58)	33 (26-52)	0.760#
Postoperative IOP (mmHg)	14 (8-38)	28 (23-38)[a]	16 (9-21)[b]	12 (8-20)[b]	<0.001#
Number of postoperative medications	1 (0-3)	3 (2-3)[a]	2 (1-3)[a]	0 (0-0)[b]	<0.001#
Type of glaucoma, *n(%)*					
POAG	17 (27.0)	3 (33.3)	6 (19.4)	8 (34.8)	0.768*
PEXG	28 (44.4)	3 (33.3)	15 (48.4)	10 (43.5)	
PACG	9 (14.3)	3 (33.3)	4 (12.9)	2 (8.7)	
Juvenile glaucoma	6 (9.5)	0 (0.0)	4 (12.9)	2 (8.7)	
Uveitic glaucoma	2 (3.2)	0 (0.0)	1 (3.2)	1 (4.3)	
Traumatic glaucoma	1 (1.6)	0 (0.0)	1 (3.2)	0 (0.0)	

Values are presented as Median (Minimum-Maximum) unless stated otherwise.
[a,b]: Different superscripts indicate a Bonferroni corrected significant difference between the two groups at 0.05 significance level.
*: Fisher's Exact Test, #: Kruskal-Wallis Test (Dunn's Test for Post-Hoc comparisons).
UBM: ultrasound biomicroscopy, POAG: primary open angle glaucoma, PEXG: pseudoexfoliation glaucoma, PACG: primary angle-closure glaucoma,

gel, Novartis Farma, Origgio, Italy), the ultrasound probe scanned over the entire filtering bleb region. Evaluations were conducted on the bleb morphology, including the maximum height of the subconjunctival filtering bleb, the intrableb reflectivity, the presence of intrableb microcysts and the route under the scleral flap, with the assesment of the patency of the internal ostium and peripheral iridectomy. The UBM images were evaluated for:

Internal reflectivity of the bleb: it was divided into three categories: low reflectivity, medium reflectivity, high reflectivity. Based on the correlation with the sclera's reflectivity, the bleb's internal reflectivity was categorized.

Bleb height: we measured the maximal height of the subconjunctival filtering bleb from the surface of the sclera to the inner surface of the filtering bleb. It was categorized into low bleb height if thickness <1 mm, medium bleb height if thickness 1-2 mm, and high bleb if thickness ≥2 mm.

The presence of intrableb microcysts: There were two grades: present and absent.

Aqueous drainage route under scleral flap: it was divided into three classes: visible, partially visible and invisible. A path was classified as visible under the scleral flap if it was seen all the way along the flap. It was categorized as partially visible if it was not visible over the whole scleral flap.

Sclerectomy site: it was separated into two distinct classes: patent or occluded.

Peripheral iridectomy: it was separated into two distinct classes: complete or incomplete.

STATISTICAL ANALYSIS

Descriptive statistics for patient/eye characteristics and UBM parameters are shown as; frequency (percentage) for categorical and median (minimum-maximum) for numerical variables respectively. Shapiro-Wilk test and graphical methods were used to assess the assumption of normality. A total of 63 eyes from 52 patients were included in the study. Less than 20% (n=11) of patients had both eyes included and the inter eye correlation for the UBM parameters between these 11 patients ranged from 0.298 to 0.444. Considering the percentage of patients with both eyes and the magnitude of intereye correlations, ignoring the dependency between the eyes may not have substantial impact on the p-values and confidence intervals[6], thus eyes from these patients were treated as independent observations. Comparisons of patient/eye characteristics and UBM parameters between the success grade groups (complete success, partially success and failure) were made using Pearson Chi-square or Fisher's Exact tests for gender, type of glaucoma, PI, IO, suture lysis, bleb reflectivity, presence of intrableb cysts, tract under scleral flep and Kruskal – Wallis test for age, pre and post operative IOP, number of post operative medications, bleb height. Due to the low number of cases in the failure group and sparseness of the data, failure and qualified success categories were combined and the effect of UBM parameters on complete success was assessed using Binary and Exact Logistic Models. The statistical analyses were performed using SAS Studio (SAS OnDemand for Academics, SAS Institute Inc.). R (RStudio 2022.02.1+461 "Prairie Trillium" Release for Windows) packages "ggplot2", "ggmosaic" and "ggpubr" were used to visualize the data. p values less than 0.05 were considered statistically significant.

RESULTS

Fifty-two patients (63 eyes) were analyzed (24 females, 28 males). Median age of the patients was 62 years (range, 22-82 years). This study examined many forms of glaucoma including primary open angle glaucoma (n=17), juvenile glaucoma (n=6), primary angle-closure glaucoma (n=9), pseudoexfoliation glaucoma (n=28), uveitic glaucoma (n=2), and traumatic glaucoma (n=1). The median time between surgery and the UBM examination was 41 months (range 2-188 months). Twenty three eyes (36.5%) had successful blebs with a median of IOP 12 mm Hg, 31 eyes (49.2%) had partially successful with a median of IOP 16 mm Hg, and 9 eyes (14.3%) had failed blebs with a median of IOP 28 mm Hg.

Intrableb microcysts were observed in 52.2% (12 of 23) of the complete successful blebs versus 22.6% (7 of 31) of the partially successful blebs. Intrableb microcysts were absent in all failed blebs (P=0.007).

A route under the scleral flap was visible in all complete successful blebs, in 87.1% (27 of 31) of the partially successful blebs and 22.2% (2 of 9) of the failed blebs (P<0.001). Sclerectomy sites were present in all patients.

The peripheral iridectomy was patent in all cases except one case (Table 2) (Figure 1a,b).

The low bleb height occurred in 77.8% (7 of 9) of the failed blebs versus 8.7% (2 of 23) of the complete successful blebs (P<0.001). The median height of successful blebs [1.4 (0.8-3.0)] was significantly higher than the partially successful blebs and failed blebs. [0.7 (0.4-1.4) ve 0.9 (0.5-2.2) respectively] (P<0.001).

Intrableb low reflectivity in complete successful blebs 60.9% (14 of 23) was significantly higher than the failed blebs 0% (0 of 9). Intrableb medium reflectivity in qualified success blebs 51.6% (16 of 31) was significantly higher than the failed blebs 0% (0 of 9). Intrableb high reflectivity in failed blebs 100% (9 of 9) was significantly higher than the successful and partially successful blebs [4.3% (1 of 23) and 19.4% (6 of 31) respectively] (P<0.001) (Figure 2).

When the UBM parameters were analyzed using binary and exact logistic model test 0.1 unit increase in the bleb height increases the likelihood of complete success by 27.1% [OR(95%CI): 1.271 (1.110 –1.455); p=0.001]. High reflectivity causes a decrease in the likelihood of complete success by 95.3% compared to eyes with low reflectivity [OR(95CI%): 0.047 (0.001 – 0.400); p=0.001]. Eyes with intrableb cysts are 4.990 times likely to have complete success compared to eyes without cysts [OR(95CI%): 4.990 (1.408 – 19.290); p=0.010] (Table 3).

Table 2. *Comparison of UBM Parameters between the success groups.*

Variable	**Total (N=63)**	**Failed (N=9)**	**Partially successful (N=31)**	**Complete successful (N=23)**	**p-value**
Thickness of bleb (μm)	1.1 (0.4 – 3.0)	0.7 (0.4 – 1.4)[a]	0.9 (0.5 – 2.2)[a]	1.4 (0.8 – 3.0)[b]	<0.001[#]
PI, *n (%)*					
Complete	62 (98.4)	8 (88.9)	31 (100.0)	23 (100.0)	0.143[*]
Incomplete	1 (1.6)	1 (11.1)	0 (0.0)	0 (0.0)	
Sclerectomy site, *n (%)*					
Present	63 (100.0)	9 (100.0)	31 (100.0)	23 (100.0)	-
Absent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Bleb height, *n (%)*					
Low	27 (42.9)	7 (77.8)[a]	18 (58.1)[a]	2 (8.7)[b]	<0.001[*]
Moderate	25 (39.7)	2 (22.2)	10 (32.3)	13 (56.5)	
High	11 (17.5)	0 (0.0)	3 (9.7)	8 (34.8)	
Bleb reflectivity, *n (%)*					
Low	23 (36.5)	0 (0.0)[a]	9 (29.0)[a,b]	14 (60.9)[b]	<0.001[*]
Medium	24 (38.1)	0 (0.0)[a]	16 (51.6)[b]	8 (34.8)[a,b]	
High	16 (25.4)	9 (100.0)[a]	6 (19.4)[b]	1 (4.3)[b]	
Cysts inside bleb, *n(%)*	19 (30.2)	0 (0.0)[a]	7 (22.6)[a,b]	12 (52.2)[b]	0.007[**]
Aqueous drainage route under scleral flap, *n(%)*					
Invısıble	5 (7.9)	5 (55.6)[a]	0 (0.0)[b]	0 (0.0)[b]	<0.001[*]
Partially visible	6 (9.5)	2 (22.2)	4 (12.9)	0 (0.0)	
Visible	52 (82.5)	2 (22.2)[a]	27 (87.1)[b]	23 (100.0)[b]	

Median (Minimum-Maximum) values for Kalınlık (birim).
[a,b]: Different letters indicate a Bonferroni corrected significant difference between the two groups at 0.05 significance level.
[*]: Fisher's Exact Test, [**]: Pearson Chi-Square Test, [#]: Kruskal-Wallis Test (Dunn's Test for Post-Hoc comparisons).
PI: Peripheral iridectomy

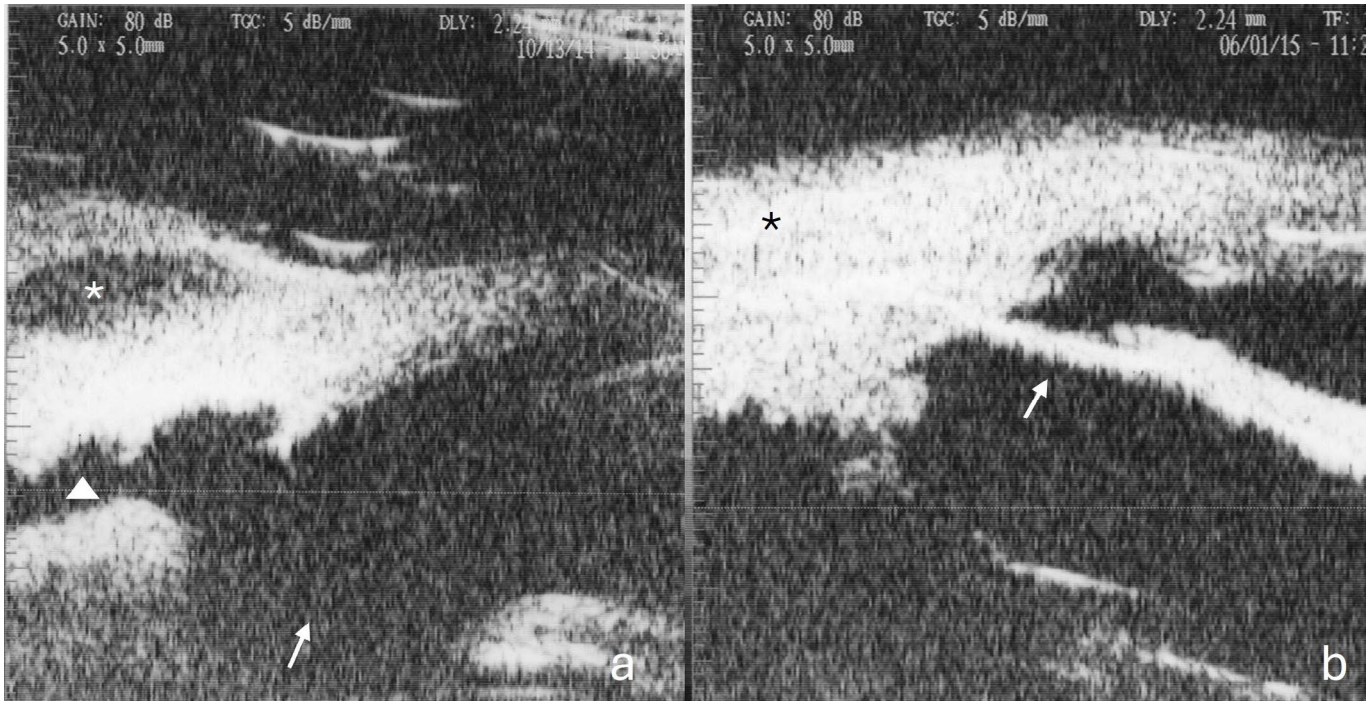

Figure 1. ***a)*** *Low reflectivity bleb (asterisk) with a visible aqueous drainage route (arrowhead) and patent peripheral iridectomy (arrow) on UBM image.* ***b)*** *High reflectivity bleb (asterisk) with a non-visible aqueous drainage route and occluded peripheral iridectomy (arrow) on UBM image*

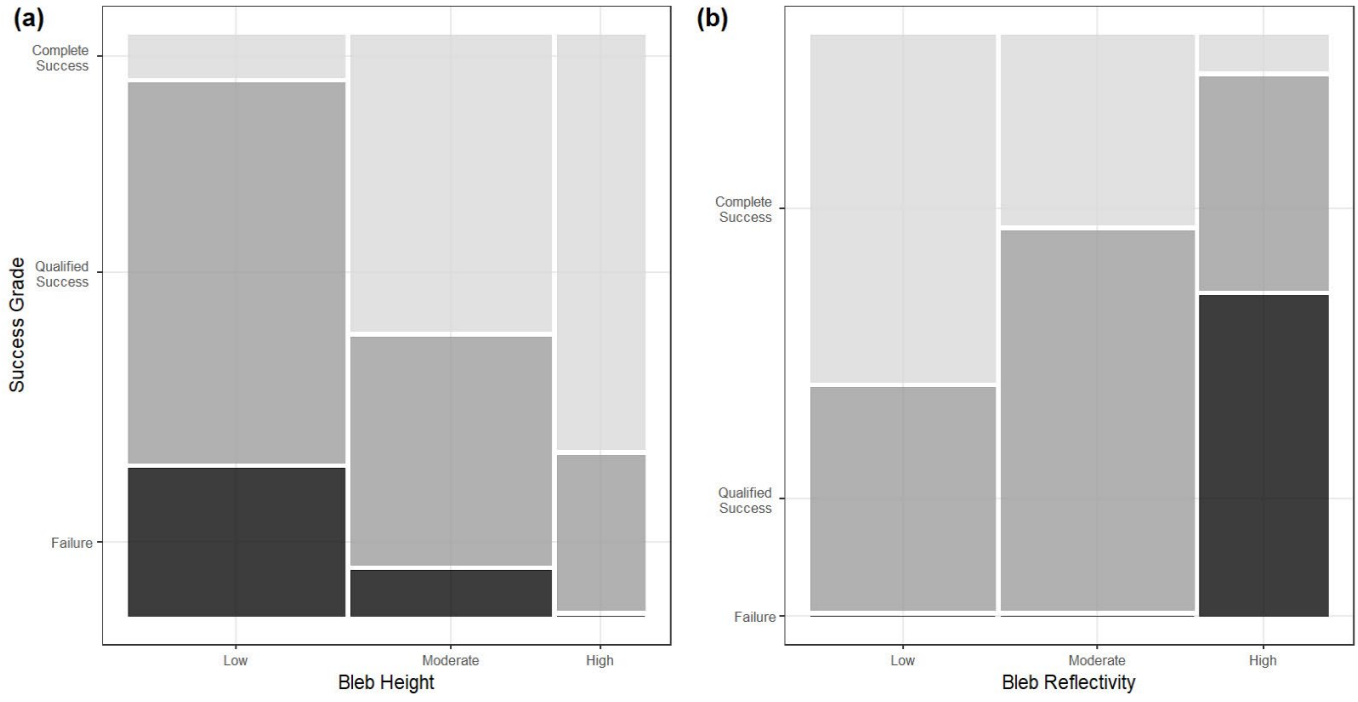

Figure 2. *Mosaic plot of success group proportions for* ***a)*** *bleb height and* ***b)*** *bleb reflectivity*

Table 3. *Parameters influencing the success of blebs*		
Variable	**OR (95% CI)**	**p- value**
Thickness of bleb (*0.1 unit increase*)[a]	1.271 (1.110 –1.455)	0.001
Bleb reflectivity[b]		
Medium	0.330 (0.082 – 1.227)	0.109
High	0.047 (0.001 – 0.400)	0.001
Cysts inside bleb (*present*)[b]	4.990 (1.408 – 19.290)	0.010

[a]: Binary Logistic Model, [b]: Exact Logistic Model
OR: Odds Ratio, CI: Confidence Internal
UBM: ultrasound biomicroscopy

DISCUSSION

Slit-lamp examination of the bleb and surrounding conjunctival tissue, along with IOP measurement are the most crucial parameters for assessing bleb function.[7] Clinical characteristics assessed under the slit lamp, such as size, height, vascularity, leakage, and encapsulation, have been used to evaluate bleb functionality.[5] Several grading systems, including Grehn bleb classification score, the Indiana Bleb Appearance Grading Scale and the Moorfields Bleb Grading System have been developed to assist clinicians during post-trabeculectomy follow-up and to assess the efficacy of filtering blebs.[8] While slit-lamp examination provides information about the conjunctival wound, it does not offer insight into the conditions beneath the scleral flap. The introduction of UBM has enabled a detailed, noninvasive evaluation of the inner architecture of blebs following trabeculectomy, thereby overcoming the limitations of traditional slit-lamp assessments.

The morphology of blebs has been the subject of numerous investigations. UBM images of functioning filtering blebs with adequate IOP control typically reveal the absence of a cavernous fluid-filled space, a visible passage beneath the scleral flap, low-to-medium bleb reflectivity, and a highly reflective bleb wall.[9-11] Yamamoto et al.[9] and Avitabile et al.[10] demonstrated that bleb height did not appear to be a significant factor in evaluating the function of filtering blebs. Conversely, El-Salhy et al.[11] reported that failed blebs had lower bleb heights. In addition, the presence of intrableb cysts was significantly associated with cases of complete surgical success. However, there was no significant correlation found between the various grades of functional success and the existence of sclerectomy or the patency of peripheral iridectomy. In a study conducted by Jinza and colleagues[12] found a significant negative correlation between postoperative IOP level and bleb height. Additionally, a significant positive correlation was observed between the thickness of the aqueous drainage pathway beneath the center of the scleral flap and the maximum height of the filtering bleb.

In this study, the thickness of the bleb, intrableb reflectivity, and the presence of cysts within the bleb were analysed using binary and exact logistic model. Our findings revealed that the presence of cysts within the bleb positively correlated IOP control. More precisely, a 0.1 µm increase in bleb thickness was associated with a 27.1% higher likelihood of achieving complete surgical success. Bleb scarring is the main cause of failure in filtration surgery. Thus, excessive healing of the scleral wound beneath the scleral flap may lead to reduced aqueous humor filtration and fibrotic changes in the subconjunctival tissue of the filtering bleb. Supporting this hypothesis, all cases in our study with an invisible drainage tract under the scleral flap were identified as non-functional blebs. The use of UBM to evaluate the bleb's structure and function may influence the clinical decision to utilize laser suturolysis after trabeculectomy.[13]

Ozen et al.[14] reported that functional blebs associated with good IOP control were characterized by greater visibility of the aqueous drainage route under the scleral flap, lower bleb reflectivity, and greater bleb height. They found that high bleb reflectivity on UBM imaging in unsuccessful blebs was associated with increased fibrosis. These findings consistent with our study emphasizing the significance of aqueous drainage under the scleral flap as a critical factor for surgical success. Additionally, the presence of intrableb microcysts, lower reflectivity, and increased bleb height were strongly correlated with successful surgical outcomes, whereas high reflectivity and reduced bleb height were associated with functional failure. These findings provide valuable guidance for clinicians, enabling improved postoperative management strategies and early detection of potential complications.

STUDY LIMITATIONS

The study has several limitations due to its single-center design, small sample size, heterogenous group of patients

(primary open angle glaucoma, juvenile glaucoma, pseudoexfoliation glaucoma, primary angle closure glaucoma, secondary glaucoma after uveitis, traumatic glaucoma) and the large range of time between surgery and UBM examination (2-188 months).

CONCLUSION

This study highlights the utility of UBM in analyzing the morphology of filtering blebs. In conclusion, this study demonstrates that the internal morphology of filtering blebs can be effectively visualized and analyzed using UBM. Ultrasound biomicroscopy may be a helpful tool to decide on the appropriate management method for bleb revision. The combining imaging and clinical data provides a novel perspective for understanding surgical outcomes following trabeculectomy. This information may be useful in improving surgical methods and assessing the applicability of various adjuvant therapies in the surgical management of patients with glaucoma.

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