Predictors of Bubble Formation and Type Obtained With Pneumatic Dissection During Deep Anterior Lamellar Keratoplasty in Keratoconus

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• PURPOSE: To identify predictors of bubble formation and type during big-bubble deep anterior lamellar keratoplasty (BB-DALK) performed in keratoconus at different stages of severity.

• DESIGN: Retrospective Cohort Study.

• METHODS: SETTING: University Magna Græcia (Catanzaro, Italy); STUDY POPULATION: Consecutive keratoconus patients undergoing BB-DALK from September 2014 to February 2019. OBSERVATION PROCEDURE: Keratometric astigmatism, mean keratometry value (K-mean), highest keratometry value (K-max), thinnest point, anterior segment optical coherence tomography (AS-OCT)–based stage of ectasia. MAIN OUTCOME MEASURES: Rate of bubble formation and type; number and fate of micro-/macroperforation; conversion to mushroom keratoplasty (MK); comparison of parameters in patients with bubble formation vs failure and in type 1 vs type 2 bubble; areas under the curves (AUC) of preoperative parameters for distinguishing between bubble types.

• RESULTS: Pneumatic dissection succeeded in 113 of 155 eyes (72.9%), with 100 type 1 bubbles (88.4%), 11 type 2 (9.8%), and 2 mixed-type (1.8%). Microperforations were managed conservatively in type 1 bubbles; macroperforations occurring in both types of bubbles required conversion to MK. Preoperative K-mean and K-max values were significantly higher in eyes in which bubble formation succeeded (respectively, $P = .006$ and $P < .013$). Type 1 bubbles formed in eyes with significantly lower age, K-mean, and AS-OCT stages and higher pachymetric values (always $P < .029$). Age had the highest diagnostic power for discrimination between bubble types, followed by AS-OCT stage, pachymetry, K-mean, and astigmatism (respectively, AUC = 0.861, 0.779, 0.748, 0.700, 0.670).

• CONCLUSIONS: Older age and advanced stages of keratoconus were predictors of type 2 bubble formation during BB-DALK that was associated with an increased risk of complications. (Am J Ophthalmol 2020;212:127–133. © 2019 Elsevier Inc. All rights reserved.)

CHARACTERIZED BY PROGRESSIVE CORNEAL THINning, protrusion, and irregular astigmatism, keratoconus (KC) is the most common corneal ectasia, and, in its early stages, can be managed adequately by spectacle or contact lens correction.[1–6] However, in cases of reduced visual acuity secondary to corneal scarring, contact lens intolerance or uncorrectable high-degree irregular astigmatism, a surgical intervention is mandated.[7] Deep anterior lamellar keratoplasty (DALK) is increasingly reported as a technique used to treat corneal stromal pathologies with healthy endothelium and, being essentially an extraocular intervention, DALK not only eliminates endothelial rejection but also reduces the risks associated with "open-sky" surgery.[8–12] The most widely used technique to perform DALK is the big-bubble (BB-DALK), as described by Anwar and Teichmann, during which injection of air in the deep stroma results in cleavage of the deep stroma from either the pre-Descemet layer (PDL) or Descemet membrane (DM).[13] This natural plane of separation avoids the interface irregularity that can be associated with manual dissection.[14]

Recent studies have demonstrated that the cleavage plane obtained during pneumatic dissection differs, with 3 possible types of air bubble created.[15] A type 1 bubble (the most common) originates from the center of the cornea, extending radially, and represents a plane of separation between the deep stroma and the PDL, whereas a type 2 bubble originates from the periphery and extends centripetally, forming between PDL and DM. Finally, both bubbles may coexist to form a mixed bubble. The corresponding outcomes of BB-DALK depend not only on the formation or failure of the bubble, but also on the

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type of bubble itself. For example, since the floor of a type 2 bubble consists only of DM, it carries a high risk of perforation, which can mandate conversion to full-thickness penetrating keratoplasty (PK). Furthermore, even in the absence of perforation, the occurrence of a type 2 bubble has recently been associated with an increased risk of postoperative double anterior chamber formation requiring further intervention.[16] Formation of a type 2 bubble increases, therefore, the intraoperative challenge of DALK, and the identification of predictive factors correlating with its occurrence may help improving the outcomes of DALK.

The aim of this study was to investigate whether statistical analysis of preoperative demographic and clinical parameters may succeed in predicting the success of pneumatic dissection (bubble formation) in addition to the type of bubble obtained with it in keratoconic corneas undergoing DALK.

METHODS

• **STUDY DESIGN:** In this institutional retrospective cohort study, the records of all consecutive DALK procedures performed in patients affected by KC at a tertiary referral center (Department of Ophthalmology, University of Magna Græcia, Catanzaro, Italy) from September 2014 to February 2019 were reviewed. The study followed the tenets of the 2013 Declaration of Helsinki and was approved by the local Ethics Committee (Comitato Etico Università Magna Graecia of Catanzaro, Italy). Informed consent was obtained from all patients undergoing surgery. Patients who did not gain useful visual acuity with spectacles or contact lens were considered candidates for surgery. Eyes with previous hydrops or evident lesions of DM were excluded. Preoperatively, all patients underwent a complete ophthalmologic evaluation including slit-lamp examination; corrected distance visual acuity (CDVA), expressed both in logarithmic units of the minimum angle of resolution (logMAR) and in Snellen fraction; refraction; tonometry; funduscopy; endothelial specular microscopy (EM-3000; Tomey, Erlangen, Germany); and anterior segment optical coherence tomography (AS-OCT) (Casia; Tomey, Tokyo, Japan).

• **PREOPERATIVE DATA COLLECTION:** The following preoperative data were collected for the statistical analysis: age; sex; keratometric astigmatism; K-mean; K-max; thinnest pachymetric measurement; and severity of disease, graded according to a previously described AS-OCT classification[17]: stage 1, thinning of apparently normal epithelial and stromal layers at the conus; stage 2, hyperreflective anomalies occurring at the Bowman layer level with epithelial thickening at the conus, without or with stromal opacities (2a and 2b, respectively); stage 3, posterior displacement of the hyperreflective structures occurring at the Bowman layer level with increased epithelial thickening and stromal thinning, without or with stromal opacities (3a and 3b, respectively); stage 4, pan-stromal scar; stage 5, hydrops, acute onset or healing phase (5a and 5b, respectively).

• **SURGICAL PROCEDURE:** Surgery was performed in all eyes by a single surgeon (V.S.); anesthesia and akinesia were obtained by means of peribulbar injection of 10 mL of a 0.75% ropivacaine solution in all cases but 5, who received general anesthesia. As described previously in detail,[18] pharmacologic mydriasis was induced in all eyes before starting surgery; after, the geometric center of the cornea was marked and a disposable Hessburg-Barron suction trephine (Katena Products Inc, Denville, New Jersey, USA) was used to create circular incision in the recipient cornea between 8.75 and 9 mm in diameter. The peripheral pachymetric map obtained before surgery by means of the Casia corneal topographer serve as a reference for the trephination of approximately 80% of the total corneal thickness in depth. Pneumatic dissection was attempted by advancing first a dedicated probe and then a cannula up to 2-3 mm centripetally from the bottom of the deep trephination. Regardless of the success of pneumatic dissection, in all cases the recipient cornea was debulked by performing an anterior keratectomy, which removed about 80% of the anterior stroma; even when the residual bed was very thin, this thickness was sufficient to prevent the viscoelastic device (OVD) from breaking through to the surface. When pneumatic dissection succeeded, adhesive viscoelastic substance (IAL-F; Fidia, Padova, Italy) was laid centrally onto the bubble roof and a 15-degree blade was used to enter the bubble. The inferior arm of a blunt Vannas scissor was inserted into the collapsed bubble through the slit obtained with the 15-degree blade, which was enlarged to allow completion of the removal of the bubble roof by means of corneal scissors. In case of bubble smaller than 8.75 to 9.00 mm in diameter, opening of the bubble roof was extended only up to the white peripheral ring formed by the air injection; then, a blunt dissector (Galan stromal dissector spatula; Janach, Como, Italy) was used to gently enlarge the dissection up to the trephination edge, thus allowing a safer removal of the remaining tissue crown. When a mixed bubble formed, only the type 1 part was opened, leaving the type 2 part untouched and simply waiting for air to reabsorb postoperatively. When pneumatic dissection failed, the procedure was continued, attempting injecting ophthalmic viscoelastic device (I.SPACE sodium hyaluronate 1.55%; Laboratoires Vivacy, La Ravoire, France) through a cannula inserted into the same stromal path used for pneumatic dissection, according to the surgical steps previously described.[19] If also OVD-assisted dissection failed, layer-by-layer manual dissection was performed aiming at reaching a level in the deep stroma free from all microbubbles. The donor

TABLE 1. Comparison of Demographic and Clinical Parameters of Patients According to the Success or Failure of Bubble Formation and Type of Bubble Formed During Deep Anterior Lamellar Keratoplasty

		Bubble Success			Bubble Type		
Parameter	Overall (N = 155)	Formation (n = 113)	Failure (n = 42)	*P*	Type 1 (n = 100)	Type 2 (n = 11)	*P*
Age (years)	41.4 ± 15.7	41.7 ± 15.9	40.3 ± 15.2	.704	39.5 ± 15.1	58.7 ± 8.7	<.001*
Sex (male/female)	87/68	69/49	18/19	.293	60/45	7/4	.678
Keratometric astigmatism (D)	4.9 ± 3.0	5.0 ± 3.0	4.5 ± 2.8	.258	5.1 ± 3.0	3.6 ± 3.0	.065
K-mean (D)	62.9 ± 8.6	64.0 ± 8.4	59.4 ± 8.3	.006*	63.4 ± 8.2	69.4 ± 8.8	.029*
K-max (D)	66.2 ± 9.4	67.2 ± 9.2	62.7 ± 9.3	.013*	66.8 ± 9.1	71.9 ± 9.9	.091
Thinnest point (μm)	350.1 ± 75.2	346.1 ± 72.5	362.8 ± 83.1	.181	353.8 ± 67.5	279.2 ± 88.2	.007*
AS-OCT classification				.441			.002*
Stage 1	22 (14.2%)	14 (11.9%)	8 (21.6%)		14 (13.3%)	0 (0.0%)	
Stage 2a	53 (34.2%)	42 (35.6%)	11 (29.7%)		40 (38.1%)	1 (9.1%)	
Stage 2b	18 (11.6%)	12 (10.2%)	6 (16.2%)		10 (9.5%)	2 (18.2%)	
Stage 3a	16 (10.3%)	15 (12.7%)	1 (2.7%)		15 (14.3%)	0 (0.0%)	
Stage 3b	27 (17.4%)	21 (17.8%)	6 (16.2%)		16 (15.2%)	4 (36.4%)	
Stage 4	19 (12.3%)	14 (11.9%)	5 (13.5%)		10 (9.5%)	4 (36.4%)	

AS-OCT = anterior segment optical coherence tomography; D = diopters; DALK = deep anterior lamellar keratoplasty; K-max = highest keratometry value; K-mean = mean keratometric value.

Statistically significant *P* values are indicated by an asterisk (*).

cornea was punched from the endothelial side with a Barron donor punch (Katena Products Inc) of the same diameter of the trephine used on the recipient cornea. Then, after staining with 0.06% trypan blue dye (VisionBlue; D.O.R.C., Zuidland, The Netherlands), DM and endothelium was gently stripped off using a dry Weck-Cel sponge. Four interrupted 10-0 nylon sutures secured the graft into the recipient bed and surgery was completed with 2 running 10-0 nylon sutures of 16 bites each. Starting the following day, betamethasone 0.2% and chloramphenicol 0.5% eye drops were administered every 2 hours, then were tapered off to a single daily steroidal administration 1 month after partial suture removal and finally discontinued at month 6 after surgery.

• **INTRAOPERATIVE PARAMETERS:** The following intraoperative data were recorded for each surgery: bubble formation (obtained by means of air or OVD injection); bubble type; micro- or macroperforations; conversion to mushroom keratoplasty (MK).

• **STATISTICAL ANALYSIS:** SPSS statistical software (SPSS Inc, Chicago, Illinois, USA) was used for data analysis. Values were expressed as mean ± standard deviation (SD). The Mann-Whitney *U* test was used to compare continuous and ordinal variables between cases with bubble formation vs bubble failure and cases with type 1 vs cases with type 2 bubble formation. Receiver operating characteristic (ROC) curves with calculations of the area under the curve (AUC) were used to describe the accuracy of each parameter for discriminating type 1 and type 2 bubbles; for the statistical analysis, the cases of mixed-type bubble were included in the group of type 2 bubble. Sensitivity and specificity of each parameter were determined for the cutoff value whose corresponding point on the ROC curve was nearest to the coordinate (0, 100). A multivariate binomial logistic regression was performed to predict the likelihood of a type 1 bubble; a P value $< .05$ was considered statistically significant.

RESULTS

A TOTAL OF 155 CONSECUTIVE KERATOCONIC EYES OF 143 patients undergoing DALK were included in the study; the corresponding demographic and clinical characteristics are reported in Table 1. Although they were not considered exclusion criteria, none of the eyes included in this study had undergone corneal cross-linking or intracorneal ring[1] implantation. Pneumatic dissection succeeded in 113 of 155 eyes (72.9%). Type 1 bubble was obtained in 100 of 113 eyes (88.4%), type 2 in 11 of 113 eyes (9.8%), and mixed type in 2 of 113 eyes (1.8%). OVD-assisted dissection succeeded in 25 of the remaining 42 cases (59.0%) in which pneumatic dissection had failed. In the type 1 group, a microperforation occurred in 5 eyes (5%); this was addressed conservatively by air fill of the anterior chamber, with a single case of macroperforation (1%) requiring conversion to a mushroom-shaped PK. In the type 2 group, we recorded only macroperforations (2 eyes, 18.1%), both of them requiring conversion to MK. Manual dissection was completed in the remaining 17 eyes. Among

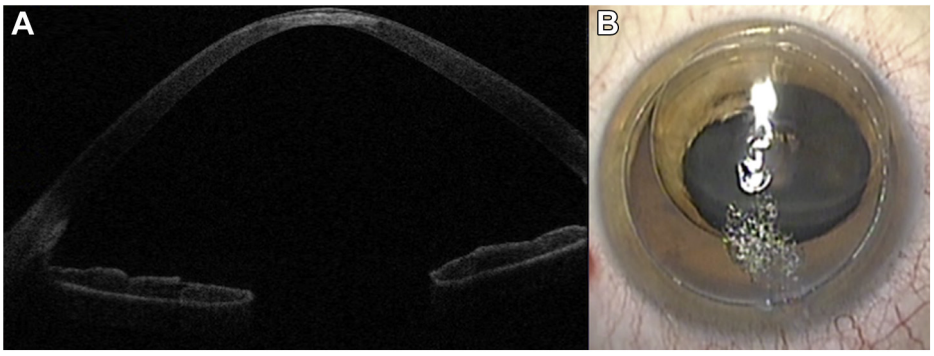

FIGURE 1. Representative images from a patient with severe keratoconus. A. Anterior segment optical coherence tomography scan of a patient with severe keratoconus (stage 4) showing a pan-stromal scar. B. Intraoperative image of type 2 bubble formation during pneumatic dissection in the same patient.

these, microperforations occurred in 2 eyes (11.7%), none requiring conversion to MK.

The preoperative K-mean and K-max values were significantly higher in cases with bubble formation (respectively, $P = .006$ and $P = .013$), while no significant differences were found preoperatively for age, sex, keratometric astigmatism, AS-OCT classification, and thinnest point between cases with bubble formation and failure (always $P > .05$, Table 1).

Cases in which a type 1 bubble was formed showed a significantly lower age ($P < .001$), lower K-mean ($P = .029$), higher thinnest point ($P = .007$), and lower stage of AS-OCT classification ($P < .002$) compared to those in which a type 2 bubble was achieved (Table 1). Figure 1 shows a representative case of a type 2 bubble occurring in a patient with severe KC (AS-OCT classification stage 4).

Eyes in which pneumatic dissection succeeded showed significantly higher values of K-mean (63.5 ± 8.5 diopters [D] vs 57.7 ± 5.2 D), K-max (66.8 ± 9.2 D vs 61.1 ± 5.9 D), and lower values of thinnest point (351.3 ± 69.9 μm vs 387.8 ± 59.5 μm) compared to those in which OVD dissection was achieved. Conversely, no significant differences in age, sex, keratometric astigmatism, and AS-OCT stage were found between the 2 groups ($P > .05$).

The ROC curves of age, keratometric astigmatism, K-mean, thinnest point, and AS-OCT stage for discriminating type 1 and type 2 bubbles are shown in Figure 2, A. Table 2 reports the AUC values of ROC curves with 95% confidence intervals, cutoff values, sensitivity, and specificity. Age had the highest diagnostic power for the discrimination between type 1 and type 2 bubble (AUC = 0.861), followed by AS-OCT stage (AUC = 0.779), thinnest point (AUC = 0.748), K-mean (AUC = 0.700), and keratometric astigmatism (AUC = 0.670).

A binomial logistic regression was performed to ascertain the effects of age, keratometric astigmatism, and AS-OCT stage on the likelihood of bubble type formation. To avoid multicollinearity, K-mean and thinnest point were not included in the regression model, since they were strongly correlated with the AS-OCT stage (respectively, R = 0.675 and R = -0.690, both $P < .001$). The logistic regression model was statistically significant, $\chi^2(3) = 28.098$, $P < .001$. The model explained 46.2% (Nagelkerke R^2) of the variance in the type of bubble and correctly classified 91.4% of cases. The ROC curve of the regression model is shown in Figure 2, B. The AUC was 0.916 (95% confidence interval: 0.825 to 1), with a sensitivity of 90.9% and a specificity of 89.5%.

Increasing age and more advanced AS-OCT stages were associated with an increased likelihood of type 2 bubble (Table 3).

DISCUSSION

OUR STUDY WAS DESIGNED TO INVESTIGATE WHETHER preoperative demographic and clinical parameters were able to predict the formation and the type of bubble during BB-DALK for KC, in order to identify potential eyes at high risk of type 2 bubble formation. Other than conventional keratometry data, clinical parameters included a novel AS-OCT-based grading system of KC.[17] This technology has been reported to be instrumental in the analysis of the progressive structural changes of the deep stroma during the evolution of the disease. These modifications often involve the precise layer into which the air is injected, and therefore may have a critical role in the success rate or type of bubble obtained by means of air injection.

In our series, preoperative maximum and mean keratometric readings values differed significantly between the 2 groups in which the bubble formed (regardless of the type) or failed, with higher values correlated with successful DALK completion. These results confirm the outcomes of previous studies reporting a higher success rate in eyes with advanced KC, where the more ectatic tissue allows

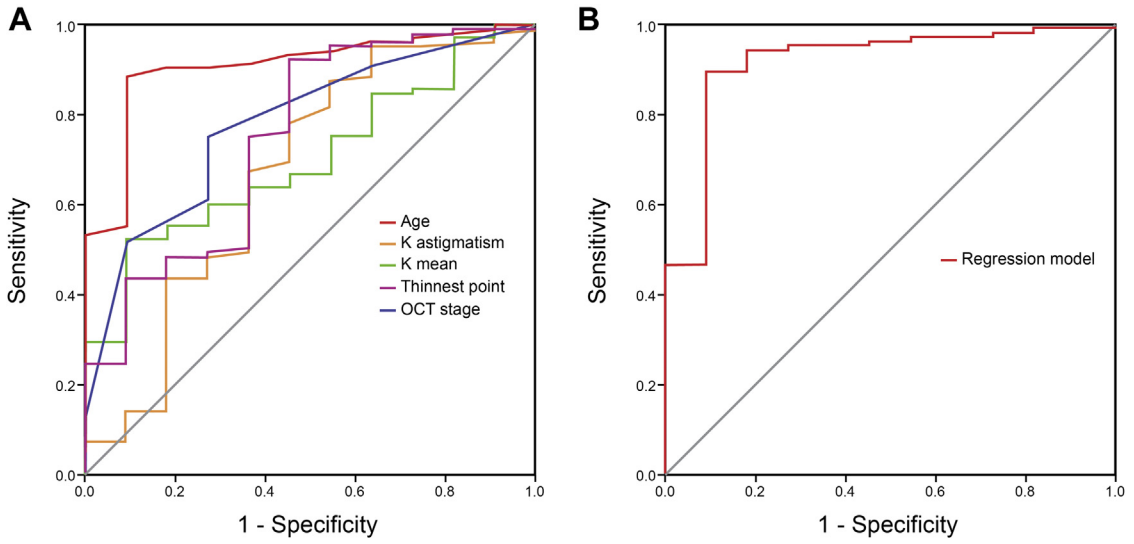

FIGURE 2. Receiver operating characteristic (ROC) curves for discriminating type 1 and type 2 bubbles. A. ROC curves of age, keratometric astigmatism, K-mean, thinnest point, and anterior segment optical coherence tomography (AS-OCT) stage. B. ROC curve of the multivariate logistic regression model including age, corneal cylinder, and AS-OCT stage as independent variables.

TABLE 2. Areas Under the Curves With 95% Confidence Intervals, Sensitivity, and Specificity of Parameters for the Discrimination Between Type 1 and Type 2 Bubbles

Parameter	AUC	95% CI	Cutoff Value	Sensitivity (%)[a]	Specificity (%)[a]
Age	0.861	0.773 to 0.949	55.5 years	83.9	90.9
Keratometric astigmatism	0.670	0.476 to 0.864	3.6 D	67.6	63.6
K-mean	0.700	0.567 to 0.834	63.9 D	60.0	72.7
Thinnest point	0.748	0.586 to 0.910	307.5 μm	75.2	63.6
AS-OCT classification	0.779	0.649 to 0.910	Stage 3a	75.2	72.7

AS-OCT = anterior segment optical coherence tomography; AUC = area under the curve; D = diopters; K-mean = mean keratometric value.
[a]Sensitivity and specificity were determined at the cutoff value whose corresponding point on the receiver operating characteristic (ROC) curve was nearest to the coordinate (0,100).

an easier access to a deeper plane, usually revealed by a sudden decrease of tissue resistance to the advancement of the cannula.[20–23] Conversely, eyes with milder stages of KC, where the failure of pneumatic dissection was higher, might benefit from OVD injection through the same track that was used unsuccessfully for the air injection bubble.[19,24]

Several parameters, including age, K-mean, thinnest point, and AS-OCT staging, differed significantly between cases in which type 1 bubble occurred compared to type 2 bubble. In particular, milder stages of KC (higher pachymetric values, lower K-mean, and early AS-OCT stages from 1 to 3a), in addition to younger age, were associated with type 1 bubble formation. This correlation between age and bubble type occurrence, here reported for the first time, may suggest that the PDL may undergo changes with aging, similarly to DM, which is modified by the formation of advanced glycation end products, with alterations in its biophysical properties.[23] However, to date, all in vitro studies examining the PDL were carried out in adult eyes, and therefore histologic data pertaining to younger eyes are not yet available. The reason for which previous studies have not identified an association between age and bubble type is likely to be related to the heterogeneous etiologic inclusion criteria applied in such studies, with a heavier skew toward older patients when including non-KC-related disease.[21] In our analysis, the cutoff value of 55 years had the highest values of sensitivity and specificity for the discrimination of bubble type occurrence. However, further histopathology studies are required to detect the possible variations occurring at a cellular level in the PDL in relation to both patient's age and severity of KC.

In our series we found the involvement of posterior corneal surface (AS-OCT stage 3b onward) to be a significant risk factor for type 2 bubble formation. We hypothesize that the deep scarring may fuse the PDL to the posterior

TABLE 3. Multivariate Logistic Regression Predicting the Likelihood of Occurrence of a Type 1 Bubble Based on Age, Keratometric Astigmatism, and Anterior Segment Optical Coherence Tomography Classification

Parameter	B	Odds Ratio	95% CI	*P*
Age	−0.078	0.925	0.874 to 0.979	.007*
Keratometric astigmatism	0.309	1.362	0.973 to 1.906	.072
AS-OCT classification	−0.753	0.471	0.280 to 0.790	.004*

AS-OCT = anterior segment optical coherence tomography.
Statistically significant *P* values are indicated by an asterisk (*).

stroma or degrade the PDL itself, preventing type 1 bubble formation owing to the direct air dispersion at the level of DM. Recently, posterior stromal scars, resulting from different corneal diseases, have been associated with the failure of pneumatic dissection,[21,22] and this poor prognostic value was found to be stronger in patients with KC compared to other corneal pathologies.[21] Accordingly, in order to homogenize our outcomes and eliminate multiple variables, we enrolled in this study only keratoconic patients.

We are aware that intraoperative variables such as the depth of placement of the cannula during pneumodissection may influence the success rate of the surgery. Therefore, we decided to analyze data obtained from a single-surgeon experience that used a reproducible approach to reach the predescemetic stroma based on a deep trephination.[18] However, a further prospective study is needed to validate in a second subset the predictive factors detected in this work.

When performing pneumatic dissection, type 1 bubble formation is desirable because the floor of the bubble includes PDL, providing strength to the thin layer and reducing the risk of perforations, which are usually small and manageable conservatively. In comparison, the type 2 floor is fragile, consisting only of DM, and, despite recent techniques proposed to optimally manage this bubble,[25,26] the completion of DALK surgery remains a challenge, with conversion to PK often needed. It is therefore unsurprising that in this series the conversion rate to MK is also much higher in the group of patients with a type 2 bubble than those with a type 1 bubble (18.1% vs 1%). In order to reduce the rate of perforation, different surgical techniques could be suggested as a safer alternative to conventional big-big-bubble DALK, such as diamond knife–assisted or pachimetry-guided manual techniques.[27,28] Another choice could be not to postpone the surgery too much, thus performing surgery in less advanced stages of KC, in which type 1 bubble is more likely to occur.

In conclusion, this study highlighted that during DALK for KC, the combination of age and stage of disease predicts the type of bubble to be obtained. Specifically, advanced stages of the disease detected by AS-OCT and increasing age were found to be strong predictors of the occurrence of type 2 bubble. Therefore, a detailed preoperative assessment of KC may provide useful information for the surgical planning of DALK in terms of both timing and technique employed. Early surgical intervention should be considered in such cases before the development of deep stromal scarring associated in BB-DALK with subsequent type 2 bubble formation and increased risk of conversion to PK. On the other hand, in severe KC cases, the use of manual techniques can be taken into account.

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