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ORIGINAL PAPER

Postoperative retinal microstructure and functional outcome after inverted-flap technique associated with silicone oil tamponade in macular hole surgery

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Abstract

Purpose: Our retrospective study on 27 patients with a large mean macular hole diameter (MH-D) of 480.08±78.62 μm evaluates the usefulness of combining the current internal limiting membrane (ILM) inverted-flap surgical technique with silicone oil tamponade, which has been associated with the classical technique of ILM peeling. *Results*: Functional results: mean visual acuity (VA) improved to 0.89±0.11 *log*Mar (logarithm of the minimum angle of resolution, at one month), 0.67±0.03 *log*Mar (at three months), 0.52±0.04 *log*Mar (at six months), 0.42±0.15 *log*Mar (at one year) postoperative (final VA), with statistical linkage between preoperative VA and final VA (two-sample *t*-test, *p*=0.007), mean MH-D and final VA (regression analysis, *p*=0.003). We compared the results by MH size (Group A ≤400 μm – eight eyes and Group B >400 μm – 19 eyes), finding statistical variance (Bonett & Levene methods). Group A presented a final VA of 0.21±0.12 *log*Mar, while Group B had 0.51±0.17 *log*Mar. Successful closure was noted in 25 (92.59%) cases, with Group A having complete closure and external limiting membrane (ELM) restoration with ellipsoid zone (EZ) regeneration in six cases. Group B had successful closure in 17 (89.47%) cases with ELM restoration in 16 cases and EZ regeneration in seven (38.88%) cases, with reintervention in two cases. Restoration of the ELM was correlated [Pearson's correlation coefficient (PCC) of 0.999, *p*=0.022] with successful closure, with overall restoration obtained in 24 (88.88%) cases and EZ regeneration in 13 (48.14%) cases. *Conclusions*: ILM inverted-flap technique with silicone oil tamponade had favorable functional and anatomical outcomes. ELM restoration was associated with successful MH closure.

Keywords: macular hole, inverted flap, ILM peeling, silicone oil tamponade.

Introduction

Full-thickness macular hole (FTMH) represent a foveal anatomical defect with interruption in all neural layers of the retina, from the internal limiting membrane (ILM) down to the retinal pigment epithelium (RPE) [1], resulting in metamorphopsia, central vision distortion [2] and reduction in measured visual acuity (VA). Vitreomacular traction is regarded as the primary leading cause in the creation of macular hole (MH) [1, 2]. Anatomic distortion of the foveal interface can be caused by anomalous posterior vitreous detachment (PVD), as defined by the *International Vitreomacular Traction Study* (IVTS) *Group* [1]. Imbalances in the degree of vitreous liquefaction and extension of posterior cortical vitreous separation from the retinal surface generate static and dynamic tractional forces in connection with the site of persistent vitreomacular adhesion (VMA) resulting in varying degrees of foveal deformation [3], influenced by the strength and size of the VMA and the intraretinal depth [3] at which surface tractional forces are dispersed. Optical coherence tomography (OCT) is indispensable to imaging the retinal microstructure and to distinguish different types of vitreomacular interface defects, for classification, surgery planning, as well as postoperative (post-op) follow-up, using image acquisition by spectral domain OCT (SD-OCT) [4], laser scanning *via* swept-source laser acquisition (SS-OCT) [5] or hybrid systems which combine both image formation methods (Figure 1). SS-OCT can visualize in greater detail the vitreomacular interface including the posterior precortical vitreous pocket (PPVP) [5]. According to Mori *et al.*, in patients with MH formation the posterior vitreous cortex can present on SD-OCT either a "smooth or wavy" surface [6, 7], with progressive increase of vitreoretinal folds as the PVD progresses. Furthermore, patients with MH formation present a degree of vitreous mobility evidenced using eye-tracking SD-OCT scans before and after performing eye movements, with vitreous separation increasing proportional to MH staging [7]. The *IVTS* Group and more recently *The European Eye Epidemiology* (E3) *Consortium* classified MH based on diameter on SD-OCT imaging as small (<250 μm), medium (>250 μm to ≤400 μm) and large (>400 μm) [1, 8, 9]. Chun & Byeon suggested a further subclassification with type A MH where vitreous traction is exerted on the foveola pulling both central Müller cell cones and *Z*-shaped Müller cells of the foveola, leading to central dehiscence with splitting and formation of foveolar pseudocysts and cleavage towards the inner margin of the Henle fiber layer [10], while in type B MH extensive traction and high VMA affects *Z*-shaped Müller cells located eccentrically on the clivus area, at distance from the foveolar floor, shearing with substantial loss of foveal tissue and posterior foveal detachment followed by hydration of the outer retina to vitreous fluid [10].

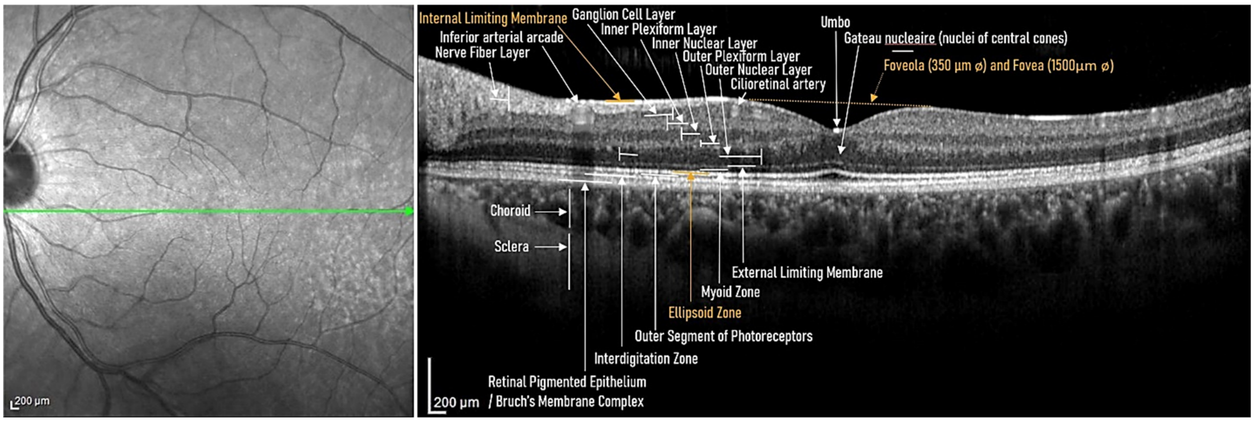


Figure 1 – ***An example of a high-resolution OCT combining swept-source and spectral domain acquisition (Heidelberg Spectralis®, Heidelberg Engineering GmbH, Heidelberg, Germany) presenting a normal eye with cilioretinal arterial anatomical variation, with annotation of the anatomical elements. Author's OCT examination, conducted in our practice on one of the author's papers and subsequently annotated by the same author with the anatomical elements. Written permission was obtained for usage of the final annotated image in the publishing of this paper. OCT: Optical coherence tomography.***

Secondary etiology for MH formation includes blunt trauma forces [8] and predisposing conditions. High myopia with posterior staphyloma favors MH formation and retinal detachment (RD) [8, 11], further presenting surgical challenges with lower visual outcomes due to decreased retinal reattachment rate and MH closure rate [11] and instability of toric intraocular lenses [12] which is notable for surgeries addressing secondary cataract formation after MH surgery. Central serous chorioretinopathy (CSC) presents impaired RPE cell function and altered choriocapillaris function [13, 14], with recently introduced adaptive optics imaging technology revealing reduced photoreceptor density and retinal microlesions [15]. Furthermore, cone photoreceptors present metabolic interaction with the RPE, such as *via* oxytocin signaling [16, 17]. These structurally weakening changes together with VMA could predispose to MH formation as described in patients with CSC [13, 14].

Several factors are important for predicting successful MH surgery. Better preoperative (pre-op) VA highly correlates with higher rates of visual gain after surgery and anatomical closure [8], while Bleidißel *et al.* reported a statistical correlation between longer symptoms duration and larger MH diameter (MH-D) [18]. Recent studies specified recovery of the external limiting membrane (ELM) could be paramount in providing subsequent functional recovery of the retina [19, 20].

The inverted-flap technique, first described in 2010 by Michalewska *et al.* [21], uses an inverted remnant flap of ILM, obtained at the moment of 360° peeling, which is then placed atop the MH defect, with the ILM side corresponding to the vitreous inverted towards the retina [21]. Compared to the established ILM peeling techniques, the inverted-flap technique currently provides better anatomical results for large (>400 µm) or refractory MH or in myopic eyes, with Chatziralli *et al.* meta-analysis reporting MH closure in 91.6–96.2% of myopic eyes with absence of RD [22] and in 94.3% of cases with concomitant RD [22]. Manipulating the ILM requires staining with Indocyanine Green solution [23], Brilliant Blue G (BBG) [24], Trypan Blue [25] or combination of BBG and Trypan Blue (Membrane Blue Dual®; DORC, Zuidland, The Netherlands) [22] or Triamcinolone Acetonide [26]. A type of tamponade must be chosen to assure the prevention of fluid leakage from the vitreous, to ensure enough tension to close the macular defect, release the subretinal fluid and assist the glial cells to migrate and close the MH [27]. Available tamponade options are gas, such as longer-lasting mixtures like Fluoroethane (C_2F_6) or Perfluoropropane (C_3F_8) or shorter-lasting mixtures like 20% or 30% Sulfurhexafluoride (SF_6) [28–30], air [31], or various densities of silicone oil [32–35]. MH post-op surgical complications include retinal breaks or RD, especially in the inferior quadrant [36], and RPE alterations [37].

Aim

Our retrospective study evaluates the usefulness of combining the current ILM inverted-flap surgical technique with silicone oil tamponade, which has been associated with the classical technique of ILM peeling in highly myopic eyes with posterior staphylomas, traumatic MH, concomitant RD, or recurrent MH pathology.

Patients, Materials and Methods

Our retrospective study enrolled 27 patients with MH, with a mean MH-D of 480.08±78.62 µm, operated by the same surgeon, at the Department of Retina within the Clinical Hospital for Ophthalmological Emergencies, Bucharest, Romania, between January 2019 and December 2020. The patients were rigorously informed before surgery of their current pathology, therapeutic options and possible or expected complications. The study received Approval from the local Ethics Committee, with written informed consent acquired from all patients. Inclusion criteria comprised patients with full-thickness medium or large (as in *IVTS* Group Classification) MH visualized on OCT, who underwent a minimum one-year post-op follow-up. Exclusion criteria were patients with insufficient follow-up, history of ocular trauma, degenerative myopia, diabetic retinopathy, age-related macular degeneration, or any previous vitreoretinal surgery.

VA was measured using a classic Snellen chart, and intraocular pressure (IOP) using a non-contact tonometer. For data accuracy, the VA was analyzed using the logarithm of the minimum angle of resolution (*log*Mar) scale. The examination was followed by a slit-lamp biomicroscopy for the assessment of the anterior segment and dilated fundoscopy. Pre-op and post-op morphological measurements were completed using the same SD-OCT system (Topcon Healthcare Solutions EMEA OY, Oulu, Finland, part of Topcon Corporation, Itabashi-ku, Tokyo, Japan). The size of the MH was defined as the horizontal diameter at the narrowest point.

Surgery was done by the same surgeon, in all cases under retrobulbar anesthesia. All patients were operated using the 25-gauge technique and instruments (Alcon Constellation® Vision System, Alcon, Fort Worth, Texas, USA). Surgery started with core vitrectomy and posterior vitreous detachment using the vitreous cutter. Triamcinolone dying was used and 360° ILM peeling (>2-disc diameters) with minimal adhesion to the MH's margins was performed. The inverted flap was done from temporal to nasal or from superior to inferior choosing the easiest approach for the surgeon's hands. Surgery was finalized using passive suction in the air-fluid exchange, averting direct manipulation or contact, and silicone oil tamponade, with patients instructed to maintain a prone position for a minimum of one day post-op.

We chose silicone oil tamponade due to several reasons impacting our current practice. Our patients are elderly with difficult cooperation and overwhelmingly present for MH late into the pathology with persistent symptoms (our study cohort presents 480.08±78.62 μm mean MH-D) and with numerous comorbidities, such as poorly treated cardiac insufficiency or hypertension, reduced pulmonary capacity and arthritis or kyphoscoliosis. Using gas tamponade, it is generally recommended that patients adopt a prone position (must avoid lying on their back) [28]. Maintaining prone positioning at least until primary closure is confirmed on subsequent post-op OCT examination presents challenges to elderly patients with medical (poorly treated cardiac insufficiency or hypertension, reduced pulmonary capacity) or functional reasons, such as arthritis or dementia [28] and foremost requires cooperation from the patient. As such maintaining the optimal prone position recommended for gas tamponade repeatedly proves difficult in our practice. Furthermore, short air or SF_6 gas tamponade presents logistical challenges for the necessary daily OCT examinations, which would allow derestricting the prone position after anatomical closure has been verified *via* OCT. Finally, due to numerous large MH (>400 μm) cases, we are more experienced in using silicone oil tamponade, which according to Pieczynski *et al.* meta-analysis is effective for primary and recurrent MH closure [38] and is proposed for resolving persistent or recurrent MH [32, 33], with the method being similar for complications with gas tamponade [38]. A thorough search of the *PubMed* and *Web of Science* databases yielded no research studies combining the current inverted-flap technique with silicone oil tamponade, further determining our research study.

The patients underwent follow-up the next day, at one week, one month, three, six and 12 months after surgery. The post-op visits consisted of a complete ophthalmological exam including VA measurement, IOP assessment, slit-lamp examination, and SD-OCT imaging. The second intervention was planned between three and six months, for all the patients and consisted of the extraction of silicone oil accompanied (or not, depending on the case) by cataract surgery. We carefully evaluated the patients for complications of silicone oil tamponade, such as inflammation [35], silicone emulsification [33, 35], elevated IOP [33] and potential development of secondary glaucoma [35].

We analyzed the resulting data by considering a successful surgical outcome the functional, anatomical, and morphological restoration of the retina. Functional improvements were defined by post-op VA improvement. Anatomical and morphological results were assessed *via* SD-OCT images. Successful outcomes consisted in restoring the ELM, ellipsoid zone (EZ) and photoreceptor layer architecture in the former MH afflicted area. For the statistical processing, we analyzed data using Statistical Package for the Social Sciences (SPSS) version 26 (IBM, Armonk, New York, USA) and Minitab 20 (Minitab Ltd., Coventry, UK).

Results

We had 27 eyes corresponding to 27 patients matching the inclusion criteria. Ten males and 17 females with a mean age of 66.4±3.21 years (range 51–79 years) and a pre-op mean VA converted in *log*Mar of 1.12±0.5. The mean MH-D was 480.08±78.62 μm (Table 1). We analyzed the distribution of patient demographics using the Anderson–Darling normality test finding no significant departure from normality (Figure 2), with a *p*-value of 0.250 (>0.05).

We analyzed the following anatomical and surgical data: pre-op mean MH-D, successful post-op closure of the MH, ELM restoration, EZ restoration, cases requiring reintervention, pre-op VA, VA at one, three, six months and one-year post-op. All VA data was previously converted into *log*MAR and tests were run using *log*MAR values. The Anderson–Darling normality test found no significant departure from normality with normal distributions for our data, with *p*-values above 0.05 (Figure 2).

Functional results (Table 1): mean VA showed statistically significant recovery at six months and one-year post-op ($p<0.001$). It improved from 1.12±0.5 *log*Mar pre-op to 0.89±0.11 at one month, 0.67±0.03 at three months, 0.52±0.04 at six months and 0.42±0.15 at one-year post-op.

Anatomical results (Table 1): successful closure was noted in 25 (92.59%) cases. Two cases needed reintervention because of the previous flap avulsion, so they received an extension of the ILM peeling, with MH closure observed at one month after reintervention. One case (of the two who needed reintervention) presented an incomplete closure of the MH, with some RPE left exposed.

We performed statistical testing using means comparison tests and linear regression analysis. We found a strong statistical link between pre-op VA and final post-op VA at one year (Figure 3), with a two-sample *t*-test returning a *p*-value of 0.007 (<0.05) and for the fitted line plot of linear regression a *R-Sq* value of 100% (Figure 3). We also noted the strong association between the mean MH-D and pre-op VA (linear regression *R-Sq* value of 100% (Figure 3), and the link between mean MH-D and final one-year post-op VA (regression analysis, *p*-value of 0.003 <0.05).

We divided the patients into two groups according to MH size to compare functional results: MH-D ≤400 μm (eight eyes, Group A) and MH-D >400 μm (19 eyes, Group B). Again, we performed the Anderson–Darling normality test finding no significant departure from normality (Figure 2) with *p*-value of 0.246 for Group A and 0.251 for Group B (both >0.05) (Figure 2). A statistically significant variance was found between Groups A and B when comparing surgical data (successful post-op closure of the MH, ELM restoration, EZ restoration, cases requiring reintervention) using Bonett & Levene tests (Bonett *p*=0.205, >0.05, Levene *p*=0.117, >0.05, Figure 4) and post-op VA at one year (Bonett *p*=0.873, Figure 4).

Table 1 – *Patient demographics and summary of post-op results*

Demographics		All patients	Group A – MH-D ≤400 μm	Group B – MH-D >400 μm
No. of patients		27	8	19
No. of eyes		27	8	19
Male patients, *n*		10	3	7
Female patients, *n*		17	5	12
Mean patient age [years]		66.4±3.21 (range 51–79)	62.6±2.79	70.2±0.42
Pre-op MH-D [μm]		480.08±78.62	324.33±54	545.66±89
Pre-op VA [*log*MAR]		1.12±0.5	0.98±0.36	1.18±0.56
Functional results		**All patients**	**Group A – MH-D ≤400 μm**	**Group B – MH-D >400 μm**
VA at one-month post-op [*log*MAR]	*p*<0.001	0.89±0.11		
VA at three months post-op [*log*MAR]		0.67±0.03		
VA at six months post-op [*log*MAR]		0.52±0.04		
VA at one-year post-op [*log*MAR]		0.42±0.15	0.21±0.12	0.51±0.17
Anatomical results		**All patients**	**Group A – MH-D ≤400 μm**	**Group B – MH-D >400 μm**
Successful post-op closure of the MH, *n* (%)		25 (92.59%)	8 (100%)	17 (89.47%)
ELM restoration, *n* (%)		24 (88.88%)	8 (100%)	16 (84.21%)
EZ restoration, *n* (%)		13 (48.14%)	6 (75%)	7 (38.88%)
Cases requiring reintervention, *n* (%)		2 (7.40%)	0 (0%)	2 (10.52%)

ELM: External limiting membrane; EZ: Ellipsoid zone; *log*MAR: Logarithm of the minimum angle of resolution; MH: Macular hole; MH-D: MH diameter; *n*: No. of cases; pre-op: Preoperative; post-op: Postoperative; VA: Visual acuity.

In Group A, pre-op mean VA was 0.98±0.36 *log*Mar, and mean MH-D was 324.33±54 μm. VA at one-year post-op has significantly improved at 0.21±0.12 *log*Mar. We obtained MH closure all cases (100%), with ELM restoration in all cases, but with EZ regeneration in only six (75%) cases (Table 1).

In Group B, pre-op mean VA was 1.18±0.56 *log*Mar, and mean MH-D was 545.66±89 μm. VA at one-year post-op has also significantly improved at 0.51±0.17 *log*Mar. We obtained MH closure in 17 (89.47%) cases, with ELM restoration in 16 cases, but with EZ regeneration in seven (38.88%) cases (Table 1).

In both groups, complete ELM restoration was found in 24 (88.88%) cases, and EZ regeneration was found in 13 (48.14%) cases, the percentage being higher in the medium MH group, as expected (Table 1).

We further explored the presence of other correlations using pairwise correlations tables (Pearson & Spearman methods, Figure 5), and confirmed strong correlation between the following variables: VA pre-op (VA pre-op) and pre-op MH-D mean [Pearson's correlation coefficient (PCC) of 1 with *p*=0.003], VA at one-year post-op and pre-op MH-D mean (PPC of 1, *p*=0.003), ELM restoration and successful post-op MH closure (PPC of 0.999, *p*=0.022) and confirmed an exactly linear relation between VA at one-year post-op and initial VA pre-op (PPC of 1, *p*-value <0.05 (noted as * by Minitab).

Weaker correlations with high *p*-values (between 0.144 and 0.189) could be noted between VA pre-op or VA at one-year post-op and mean patient age (PCC of 0.973 and 0.974, with *p*=0.144), pre-op MH-D mean and mean patient age (PCC of 0.973, *p*=0.147), VA at one year post-op and cases requiring reintervention (PCC of 0.956, *p*=0.189), however were found to have no statistical relevance (*p*-value >0.05).

Discussions

Since the first surgical techniques proposed for MH surgery by Kelly & Wendel [18, 39–40], which consisted in *pars plana* vitrectomy (PPV) followed by epiretinal membrane (ERM) peeling and use of gas-tamponade [39, 40], novel vitreoretinal techniques and a greater understanding of the pathology have achieved higher successful MH closure rates. ILM peeling technique gained a lot of popularity among vitreoretinal surgeons for the treatment of FTMH, albeit with limits to the approach of large or traumatic MH and in highly myopic eyes [41–43]. The inverted-flap technique, first described in 2010 by Michalewska *et al.* [21], uses an inverted remnant flap of ILM, obtained at the moment of 360° peeling, which is then placed atop the MH defect, with the ILM side corresponding to the vitreous inverted towards the retina [21]. Ghassemi *et al.* demonstrated that the post-op anatomical success rate is not influenced by the type of surgical technique employed [41]. The results were better than with ILM peeling alone, especially in medium, large (400–550 μm) and extra-large (>550 μm) MH, with Yamashita *et al.* obtaining in their study even a 100% rate of closure [44]. These promising results led to using this technique in traumatic MH or in patients with MH and high myopia or optic disc pit with macular detachment [45, 46]. In 2014, Michalewska *et al.* described a new technique of temporal inverted ILM flap and compared it with the "classical" method [47], obtaining similar anatomic and visual results but reducing the dissociation of the optic nerve fiber layer [iatrogenic trauma of the retinal nerve fiber layer (RNFL)] [47]. Furthermore, flap attachment to the temporal retina was improved with this technique, achieving complete macular coverage, and without flipping or detaching during air-fluid exchange [47]. The inverted-flap technique helps achieve better MH closure rates in large (>400 μm) or refractory MH or in myopic eyes (Chatziralli *et al.*: 91.6–96.2% in myopic eyes with absence of RD [22] and in 94.3% of cases with concomitant RD [22]). Finally, in our study, the anatomical closure rate was comparable at 92.59%, with ELM restoration in 24 (88.88%) cases.

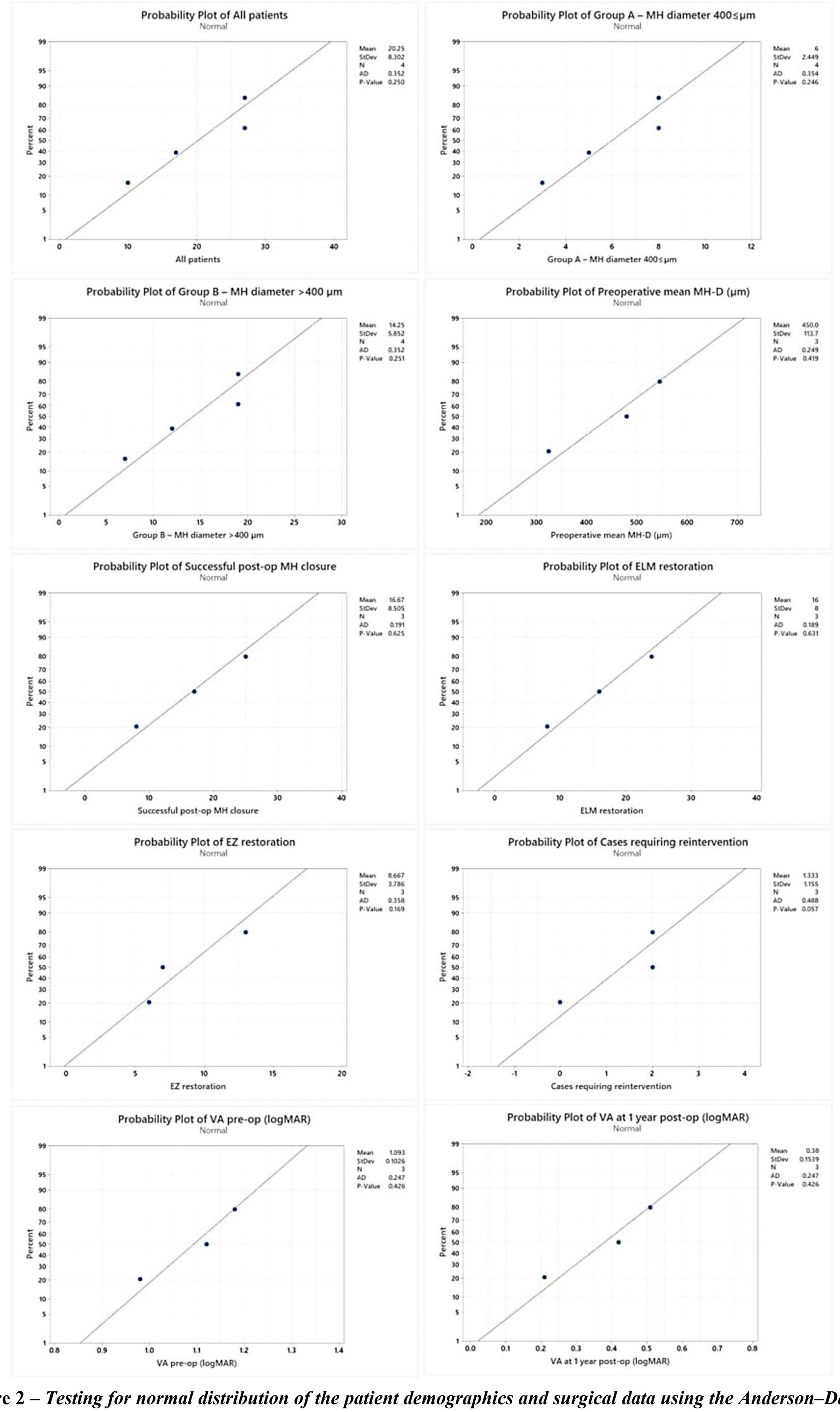


Figure 2 – ***Testing for normal distribution of the patient demographics and surgical data using the Anderson–Darling normality test finding no significant departure from normality (p>0.05), both on all patient data as well as data divided into Group A and Group B with p-value of 0.246 for Group A and 0.251 for Group B (both >0.05). ELM: External limiting membrane; EZ: Ellipsoid zone;*** **log*****MAR: Logarithm of the minimum angle of resolution; MH: Macular hole; MH-D: MH diameter; pre-op: Preoperative; post-op: Postoperative; VA: Visual acuity.***

CORRELATION

Two-Sample T-Test and CI: VA pre-op (logMAR), VA at 1 year post-op (logMAR)

Method

μ₁: population mean of VA pre-op (logMAR)
μ₂: population mean of VA at 1 year post-op (logMAR)
Difference: μ₁ - μ₂

Equal variances are not assumed for this analysis.

Descriptive Statistics

Sample	N	Mean	StDev	SE Mean
VA pre-op (logMAR)	3	1.093	0.103	0.059
VA at 1 year post-op (logMAR)	3	0.380	0.154	0.089

Estimation for Difference

Difference	95% CI for Difference
0.713	(0.373, 1.053)

Test

Null hypothesis H₀: μ₁ - μ₂ = 0
Alternative hypothesis H₁: μ₁ - μ₂ ≠ 0

T-Value	DF	P-Value
6.68	3	0.007

CORRELATION

Regression Analysis: VA pre-op (logMAR) versus VA at 1 year post-op (logMAR)

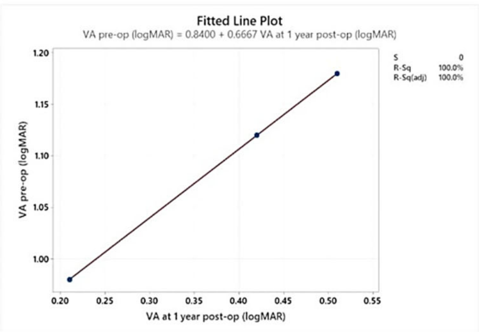
The regression equation is
VA pre-op (logMAR) = 0.8400 + 0.6667 VA at 1 year post-op (logMAR)

Model Summary

S	R-sq	R-sq(adj)
0	100.00%	100.00%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	0.0210667	0.0210667	*	*
Error	1	0.0000000	0.0000000		
Total	2	0.0210667			



CORRELATION

Regression Analysis: Preoperative mean MH-D (μm) versus VA pre-op (logMAR)

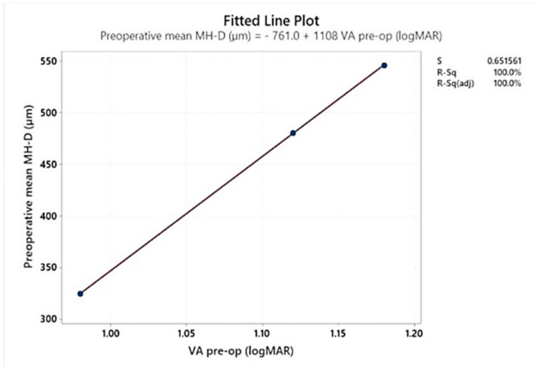
The regression equation is
Preoperative mean MH-D (μm) = - 761.0 + 1108 VA pre-op (logMAR)

Model Summary

S	R-sq	R-sq(adj)
0.651561	100.00%	100.00%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	25848.2	25848.2	60886.22	0.003
Error	1	0.4	0.4		
Total	2	25848.6			



CORRELATION

Regression Analysis: VA at 1 year post-op (logMAR) versus Preoperative mean MH-D (μm)

Regression Equation

VA at 1 year post-op (logMAR) = -0.22940 + 0.001354 Preoperative mean MH-D (μm)

Coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	-0.22940	0.00252	-90.97	0.007	
Preoperative mean MH-D (μm)	0.001354	0.000005	246.75	0.003	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.0008823	100.00%	100.00%	99.96%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	1	0.047399	0.047399	60886.22	0.003
Preoperative mean MH-D (μm)	1	0.047399	0.047399	60886.22	0.003
Error	1	0.000001	0.000001		
Total	2	0.047400			

Figure 3 – ***Comparison of pre-op VA and VA at one-year post-op, pre-op mean MH-D and pre-op VA, VA at one-year post-op and pre-op mean MH-D. The regression analysis fitted line plot models the relationship between one predictor and a continuous response and in our study highlights a direct, linear relation between pre-op VA, mean MH-D and final post-op VA at one year. A fitted line plot comparing pre-op with final post-op VA returned a linear regression a R-Sq value of 100% and a p<0.05 (noted as * by Minitab), with a two-sample*** **t*****-test between pre-op and post-op VA returning a p-value of 0.007 <0.05. A similar relation between the mean MH-D and final one-year post-op VA was found (regression analysis R-Sq value of 100%, p=0.003 <0.05). Furthermore, pre-op VA and mean MH-D were nearly interchangeable values to each other (linear regression R-Sq value of 100%, R-Sq predicted 99.96%, p=0.003) with both strongly linked to final post-op VA at one year. CI: Confidence interval;*** **log*****MAR: Logarithm of the minimum angle of resolution; MH: Macular hole; MH-D: MH diameter; pre-op: Preoperative; post-op: Postoperative; VA: Visual acuity.***

From the available tamponade options, gas with C_2F_6 or C_3F_8 or 20% to 30% SF_6 [28] is widely used with good anatomical and functional results, with Modi *et al.* concluding that SF_6 results are generally comparable to C_3F_8, with SF_6 being advantageous in providing faster return to daily routine with lesser duration of tamponade and C_3F_8 being preferred for reintervention surgeries as it provides better anatomical MH closure rates, although without translation into VA improvements [28], however with gas tamponade's recommendation of maintaining a prone position [28], with Guillaubey *et al.* finding higher closure rates (97.4% *vs* 87.5%) for patients following prone positioning indications [29]. Other studies propose alternatives, such as Hasegawa *et al.* proposed air tamponade instead of SF_6 [31] with similar closure rates (90.1% for SF_6 and 92.3% for room air) under prone positioning until anatomical closure could be confirmed *via* OCT [31], Schaub *et al.* autologous platelet concentrate and 20% SF_6 [35], while Alberti & la Cour found no statistical difference of maintaining the prone position, instead finding importance in achieving sufficient gas filling for effective closure of the MH [30]. Due to our patients presenting with large average MH-D, which pose surgical challenges in achieving anatomical closure and medical or cooperation difficulty in maintain the prone position, we approached silicone oil tamponade, which has been indicated [32–35] in persistent MHs, achieving high rates of MH closure of 92% for Lappas *et al.* [33] and 90.9% for Li *et al.* [34]. Silicone oil tamponade does not require maintaining prone positioning and allows for air travel, however, requires a second reintervention for extraction, usually within a time span of at least two months [35]. Known adverse effects include inflammation [35] and silicone emulsification [33, 35], elevated IOP [33] and potential development of secondary glaucoma [35] and accelerated nuclear sclerosis [36] with cataract formation [33]. Pieczynski *et al.* meta-analysis on the current silicone oil tamponade found good efficacy for primary and recurrent MH closure, with the method being similar for complications with gas tamponade [38], however requiring the second silicone extraction surgery [39] and indicated it as an alternative after gas tamponade [39].

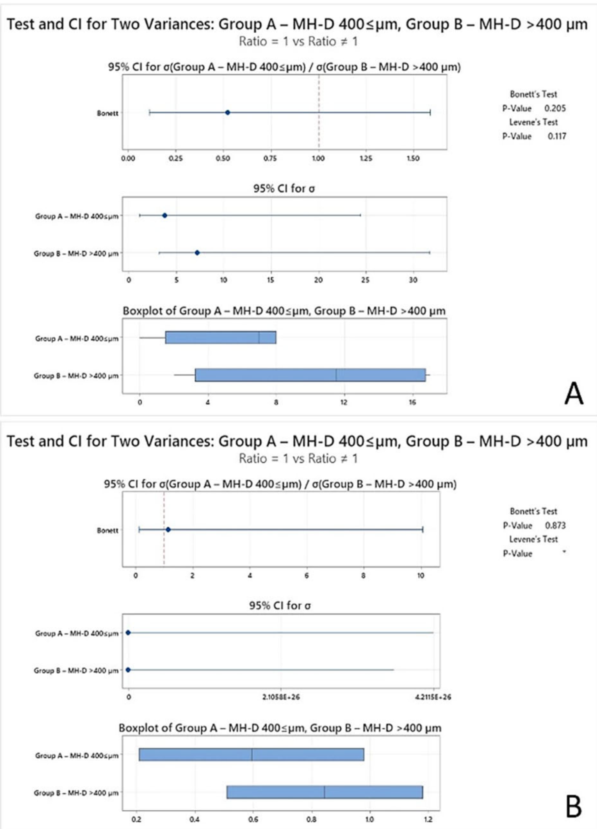


Figure 4 – ***Testing for variance between surgical data of Group A (MH-D ≤400 μm) and Group B (MH-D >400 μm) using Bonett & Levene methods: (A) A statistically significant variance was found between Group A and Group B when comparing surgical data (successful post-op closure of the MH, ELM restoration, EZ restoration, cases requiring reintervention) using Bonett & Levene tests (Bonett p=0.205 >0.05, Levene p=0.117 >0.05); (B) Statistical variance when comparing post-op VA at one year (Bonett p=0.873) between Group A and Group B. CI: Confidence interval; ELM: External limiting membrane; EZ: Ellipsoid zone; MH: Macular hole; MH-D: MH diameter; post-op: Postoperative; VA: Visual acuity.***

Correlations

	Mean patient age (years)	Preoperative mean MH-D (μm)	VA pre-op (logMAR)	Successful post-op MH closure	ELM restoration
Preoperative mean MH-D (μm)	0.973				
VA pre-op (logMAR)	0.974	1.000			
Successful post-op MH closure	0.529	0.709	0.706		
ELM restoration	0.500	0.685	0.682	0.999	
EZ restoration	0.132	0.356	0.352	0.911	0.924
Cases requiring reintervention	0.866	0.958	0.956	0.882	0.866
VA at 1 year post-op (logMAR)	0.974	1.000	1.000	0.706	0.682

	EZ restoration	Cases requiring reintervention
Preoperative mean MH-D (μm)		
VA pre-op (logMAR)		
Successful post-op MH closure		
ELM restoration		
EZ restoration		
Cases requiring reintervention	0.610	
VA at 1 year post-op (logMAR)	0.352	0.956

Pairwise Pearson Correlations

Sample 1	Sample 2	N	Correlation	95% CI for ρ	P-Value
Preoperative mean MH-D (μm)	Mean patient age (years)	3	0.973	(*, *)	0.147
VA pre-op (logMAR)	Mean patient age (years)	3	0.974	(*, *)	0.144
Successful post-op MH closure	Mean patient age (years)	3	0.529	(*, *)	0.645
ELM restoration	Mean patient age (years)	3	0.500	(*, *)	0.667
EZ restoration	Mean patient age (years)	3	0.132	(*, *)	0.916
Cases requiring reintervention	Mean patient age (years)	3	0.866	(*, *)	0.333
VA at 1 year post-op (logMAR)	Mean patient age (years)	3	0.974	(*, *)	0.144
VA pre-op (logMAR)	Preoperative mean MH-D (μm)	3	1.000	(*, *)	0.003
Successful post-op MH closure	Preoperative mean MH-D (μm)	3	0.709	(*, *)	0.498
ELM restoration	Preoperative mean MH-D (μm)	3	0.685	(*, *)	0.520
EZ restoration	Preoperative mean MH-D (μm)	3	0.356	(*, *)	0.769
Cases requiring reintervention	Preoperative mean MH-D (μm)	3	0.958	(*, *)	0.186
VA at 1 year post-op (logMAR)	Preoperative mean MH-D (μm)	3	1.000	(*, *)	0.003
Successful post-op MH closure	VA pre-op (logMAR)	3	0.706	(*, *)	0.501
ELM restoration	VA pre-op (logMAR)	3	0.682	(*, *)	0.522
EZ restoration	VA pre-op (logMAR)	3	0.352	(*, *)	0.771
Cases requiring reintervention	VA pre-op (logMAR)	3	0.956	(*, *)	0.189
VA at 1 year post-op (logMAR)	VA pre-op (logMAR)	3	1.000	(*, *)	*
ELM restoration	Successful post-op MH closure	3	0.999	(*, *)	0.022
EZ restoration	Successful post-op MH closure	3	0.911	(*, *)	0.271
Cases requiring reintervention	Successful post-op MH closure	3	0.882	(*, *)	0.312
VA at 1 year post-op (logMAR)	Successful post-op MH closure	3	0.706	(*, *)	0.501
EZ restoration	ELM restoration	3	0.924	(*, *)	0.249
Cases requiring reintervention	ELM restoration	3	0.866	(*, *)	0.333
VA at 1 year post-op (logMAR)	ELM restoration	3	0.682	(*, *)	0.522
Cases requiring reintervention	EZ restoration	3	0.610	(*, *)	0.582
VA at 1 year post-op (logMAR)	EZ restoration	3	0.352	(*, *)	0.771
VA at 1 year post-op (logMAR)	Cases requiring reintervention	3	0.956	(*, *)	0.189

Figure 5 – ***Pearson's correlation with pairwise table measuring linear correlation between two sets of data. A PCC of 1 denotes the highest correlation with a linear relationship, while a value closer to 0 denotes no linear dependency. We confirmed strong correlation between the following variables: VA pre-op and pre-op mean MH-D (PCC of 1, p=0.003), VA at one-year post-op and pre-op mean MH-D (PPC of 1, p=0.003), ELM restoration and successful post-op MH closure (PPC of 0.999, p=0.022) and confirmed an exactly linear relation between VA at one-year post-op and initial VA pre-op (PPC of 1, p<0.05, noted as * by Minitab). Weaker correlations with high p-values (between 0.144 and 0.189) could be noted between VA pre-op or VA at one-year post-op and mean patient age (PCC of 0.973 and 0.974, p=0.144), pre-op mean MH-D and mean patient age (PCC of 0.973, p=0.147), VA at one-year post-op and cases requiring reintervention (PCC of 0.956, p=0.189), however were found to have no statistical significance (p>0.05). ELM: External limiting membrane;*** **log*****MAR: Logarithm of the minimum angle of resolution; MH: Macular hole; MH-D: MH diameter; PCC: Pearson's correlation coefficient; pre-op: Preoperative; post-op: Postoperative; VA: Visual acuity.***

Functional outcomes after MH closure surgery are dependent on the restoration of the foveal structure, particularly regarding the outer retinal segment [46]. Restoration of the ELM is essential for the healing of the inner segment (IS) and outer segment (OS) junction of the photoreceptors [19] and further repair of the foveal micro-structure. The inner–outer junction of the photoreceptors (IS/OS junction) can be visualized *via* OCT and is associated with the second hyperreflective band, referred to as the inner segment ellipsoid (ISel) [20] and in the international nomenclature consensus as the EZ [48, 49]. More recently studies have pinpointing the EZ as anatomically corresponding to the photoreceptor ISel [48] (Figure 1), which is densely packed with mitochondria [48] and presents a higher refractive index, thereby inducing increased back-scattering of light that appears brighter on OCT [48] as a second hyperreflective band. Wakabayashi *et al.* reported no difference between eyes with intact ELM and either complete restoration of the IS/OS junction or disruption of IS/OS junction [50], however found both groups had significantly visual improvements measured in best corrected visual acuity (BCVA) at three months compared to patients without restoration of the ELM, which did not further progress in visual recovery and exhibited no photoreceptor IS/OS junction restoration at 12 months post-op [50]. In our study, restoration of the ELM was crucial to obtaining anatomical closure (Pearson's pairwise tables, PPC of 0.999, $p=0.022$), while restoration of the EZ was obtained with more difficulty (13 cases, 48.14%). It would appear that restoration of the ELM could lead to healing of the photoreceptors (and restoration of the EZ) which in turn leads to lasting visual recovery.

Furthermore, in our study, the size of the MH and the initial VA were directly related to the post-op prognosis and the functional outcome. We found a linear relation between pre-op VA, mean MH-D and final post-op VA at one year. A fitted line plot comparing pre-op with final post-op VA returned a linear regression a *R-Sq* value of 100% and a $p<0.05$ (noted as * by Minitab), with a two-sample *t*-test between pre-op and post-op VA returning a *p*-value of 0.007, <0.05, Figure 3). A similar relation between the mean MH-D and final one-year post-op VA was found (regression analysis *R-Sq* value of 100%, *p*-value of 0.003 <0.05). Furthermore, pre-op VA and mean MH-D were nearly interchangeable values to each other (linear regression *R-Sq* value of 100%, *R-Sq* predicted 99.96%, $p=0.003$) with both strongly linked to final post-op VA at one year. Overall, our study reported a better VA improvement one year after surgery in the group with smaller MH-D (≤400 μm), 0.21±0.12 *log*Mar in Group A compared to 0.51±0.17 *log*Mar in Group B, with a $p<0.001$. Liu *et al.* [51] presented similar results to ours, finding improvements in patients with MH <400 μm. Furthermore, a greater percent of restoration of ELM and EZ in Group A, combined with MH closure led to a better VA. In both our groups, complete ELM restoration was found in 24 (88.88%) cases – eight in Group A and 16 in Group B, and EZ regeneration was found in 13 (48.14%) cases – six in Group A and seven in Group B, the percentage being greater in the medium MH group, as expected.

Conclusions

ILM inverted-flap technique represents the standard in treating medium and large MH. Silicone oil tamponade can provide benefits, such as long-time stability of the inverted flap, prevention of fluid leakage from the vitreous cavity, ensuring enough tension to close the macular defect and assisting glial cell migration. Our study reported favorable results of using silicone oil tamponade on patients who underwent MH closure surgery using ILM inverted-flap technique. In our study, restoration of the ELM was crucial to obtaining anatomical closure, while restoration of the EZ was obtained with more difficulty. The size of the MH and the initial VA were directly related to the post-op prognosis and the functional outcome. The possible post-op complications of silicone oil tamponade, such as intraocular inflammation, silicone emulsification, elevated IOP and potential development of secondary glaucoma were not encountered in our study.

Ethics approval and informed consent

The study was performed in line with Ethics Guidelines of the institutional and/or national Research Committee, with respect to the precepts of the 1964 Helsinki Declaration and later amendments. Written informed consent was acquired from participants of the study. An ethical review and validation for publishing of this paper were granted by the local Ethics Committee of the Clinical Hospital for Ophthalmological Emergencies, Bucharest, Romania, with specific approval for data concerning clinical patient presentation, such as previous hospital admission and history, anamnesis, clinical examination and presentation including specific ophthalmological exam and slit-lamp biomicroscopy capture data and imaging, laboratory tests, further investigations such as non-contact tonometer, OCT images and other investigations, data pertaining to the treatment undergone including surgical data, images and video, data pertaining to the post-op evolution of the patients and subsequent ophthalmological follow-up examinations, with respect to the privacy of the patients and in compliance with General Data Protection Regulation (GDPR) and local Laws.

Data availability

All data generated or analyzed during this study is included in the final manuscript.

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Competing interests

The authors declare that they have no competing interests or conflict of interests.

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