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ORIGINAL PAPER

Inverted internal limiting membrane flap technique in the surgical treatment of macular holes: 8-year experience

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Abstract
Purpose To evaluate the ellipsoid zone (EZ) structural recovery, hole closure rate, and visual acuity improvement after inverted internal limiting membrane (ILM) flap technique.
Methods Retrospective cohort of eyes affected by idiopathic macular holes (MH) that underwent pars plana vitrectomy combined with inverted ILM flap technique in a tertiary center, over an 8-year period (2011–2019). The main outcomes were the postoperative qualitative analysis of EZ structure on spectral-domain optical coherence tomography, hole closure rate, and best-corrected visual acuity (BCVA) improvement of $\geq$ 0.3 units in the logarithm of minimal angle of resolution (logMAR) scale.
Results Our study included 76 eyes of 72 patients; 65% were female, with a mean age of 70 $\pm$ 8 years-old. Median (range) follow-up was 21 (3–92) months. Hole closure rate was 92%. Structural defects in EZ were observed in 66% of closed holes (EZ atrophy in 33%, EZ disruption in 22%, and EZ thinning in 11%). The mean final BCVA was 0.5 $\pm$ 0.4 logMAR (Snellen 20/63), but visual acuity improvement occurred in 80% of the eyes. Final BCVA was significantly worse in eyes with EZ atrophy compared with eyes with EZ disruption (0.75 vs. 0.36 logMAR, p = 0.004) and EZ thinning (0.75 vs. 0.32 logMAR, p = 0.015). In multivariate regression, minimum linear diameter (OR 1.01; IC 95% 1.01–1.02) independently predicted a final BCVA (logMAR) < 0.3 units.
Conclusion Inverted ILM flap technique provided a hole closure rate above 90%, similar to previous studies. Although the modest value of the final BCVA, a significant visual acuity improvement occurred in most eyes. Structural defects of EZ were found in more than half of closed MHs after surgery. Evidence of postoperative retinal atrophy was associated with a worse visual outcome.

Keywords Macular hole · Inverted internal limiting membrane flap technique · Ellipsoid zone analysis

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Introduction

The prevalence of full-thickness macular holes (MH) ranges from 0.02 to 0.8%, with the vast majority being idiopathic [1–4]. In 1988, Gass postulated that tangential vitreomacular traction resulting in centrifugal displacement of photoreceptors was the key factor in the development of idiopathic MHs [5]. According to this theory, removing tangential vitreomacular traction was speculated to avoid the progression of the hole. In 1991, Kelly et al. [6] first reported full-thickness MH closure using vitrectomy and gas. Since then, novel surgical techniques have emerged, including internal limiting membrane (ILM) peeling [7], later modified to inverted ILM flap technique [8]. Inverted ILM flap promotes MH closure, probably by stimulating the proliferation of glial cells [9, 10].

Success rates in terms of MH closure have been in the range of 85–100% with both techniques. Using the ILM peeling technique, a 90% closure rate was described for holes smaller than 400 µm [11]. Inverted ILM flap technique has demonstrated to be effective for large (> 400 µm) MHs, myopic MHs, and MHs with retinal detachment [8, 12–14]. Several studies have suggested that the inverted ILM flap technique provides better outcomes than ILM peeling alone, particularly in large and myopic MHs [11, 15]. Nevertheless, visual outcomes have been limited compared to reported high closure rates. Limitations in visual recovery at long-term follow-up were identified in eyes submitted to the ILM peeling or inverted ILM flap procedure [16]. In fact, visual recovery is influenced by the external limiting membrane and ellipsoid zone (EZ) recovery after MH closure [17]. Qualitative analysis of EZ structure on spectral-domain optical coherence tomography (SD-OCT) after performing the inverted ILM flap technique is lacking.

The purpose of this study was to evaluate the postoperative EZ structural recovery, hole closure rate, and visual acuity improvement after inverted ILM flap technique.

Materials and methods

This study consisted of a retrospective cohort of eyes affected by idiopathic MHs that underwent pars plana vitrectomy (PPV) combined with inverted ILM flap technique and gas tamponade in a tertiary center, Centro Hospitalar Universitário do Porto, over 8 years (2011–2019). Exclusion criteria included lamellar holes, myopic and traumatic MHs, MHs with retinal detachment, previous vitreoretinal surgery, indocyanine green staining, poor quality of SD-OCT images, and follow-up less than 3 months. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Centro Hospitalar Universitário do Porto. Informed consent was obtained from all patients.

Data concerning age, gender, lens status, laterality, slit-lamp, and dilated fundus examination were collected from the patients' preoperative charts. Surgical reports were reviewed.

Best-corrected visual acuity (BCVA) was evaluated at baseline and at the end of follow-up. BCVA was recorded using a standard Snellen acuity chart and converted to the logarithm of minimal angle of resolution (logMAR) for statistical analysis. The visual acuity of count fingers, hand movements, light perception, and no light perception was set as 1.8, 2.2, 2.7, and 3.0 logMAR, respectively [18].

SD-OCT imaging (SPECTRALIS; Heidelberg Engineering, Germany) was analyzed at baseline and at the end of follow-up. MH minimum linear diameter (minimal extent of the hole), basal diameter (diameter at the level of the retinal pigment epithelium), and macular hole height (maximal distance between the retinal pigment epithelium and the vitreoretinal interface) were manually measured by one researcher (N.S.). These parameters were used to calculate the macular hole index (MHI, the ratio of the macular hole height to its basal diameter). The International vitreomacular traction study group (IVTS) classification was obtained from all cases.

Surgical procedure

All surgeries consisted of standard three-port 23-gauge PPV (Constellation; Alcon.) performed by the experienced vitreoretinal surgeons (N.F., B.P., N.C., M.B., A.M.) of the Department of Ophthalmology of Centro Hospitalar Universitário do Porto. Combined vitrectomy and cataract surgery was performed at the surgeons' discretion. After core vitrectomy, the posterior vitreous detachment was induced when the hyaloid was attached, and peripheral vitreous was also removed. Inverted ILM flap technique was executed according to the method described by Michalewska et al. [8] Epiretinal membranes (ERM) were peeled before ILM peeling. ILM was peeled off in a circular mode for approximately 2 disc diameters around the MH following membrane staining with ILM-blue dye (DoubleDyne®). An ILM remnant (flap) left anchored on the edge of the MH was inserted into the hole. After fluid–air exchange, the air was replaced by a nonexpansile mixture of sulfurhexafluoride (SF6) or perfluoropropane (C3F8) gas. Patients were instructed to maintain a face-down position for a week after surgery.

Study primary outcomes

The main anatomical outcomes were the hole closure rate and the qualitative analysis of EZ structure on SD-OCT. The main functional outcome was BCVA (logMAR) improvement of ≥ 0.3 units (equivalent to 15 letters).

The hole was considered closed if there was no neurosensory defect at the fovea. The flat open appearance was excluded from the definition of closed MH. Successfully repaired MHs were categorized into two SD-OCT patterns: U-type (normal foveal contour) and V-type (steep foveal contour) [19].

For closed holes, the aspect of EZ line was evaluated on SD-OCT. Structural defects of EZ were classified as EZ thinning, EZ disruption, or EZ atrophy. EZ thinning was defined as decreased hyper-reflectivity of continuous EZ line, EZ disruption as discontinuous ellipsoid line leaving a hyporeflective space in its location, and EZ atrophy as loss of EZ line in association with outer retinal atrophy and choroidal hypertransmission. When this classification was not suitable, the closed MHs were settled as unclassified. SD-OCT analysis was performed by two retinal experts (A.M. and M.B). In case of disagreement, a third investigator (N.C.) was referred for a final decision.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc, Chicago, IL). Normal distribution was checked using the Shapiro–Wilk test or skewness and kurtosis. Categorical variables were compared with the fisher's exact test or the Chi-square test, as appropriate. Parametric or nonparametric tests including Student's t test, Mann–Whitney U test or Wilcoxon signed-rank test were used for continuous variables comparison, according to the normality of data. Post hoc analysis was performed with Bonferroni correction. Binary logistic regression was used to determine whether the variables were significant predictors of postoperative BCVA. All reported P values are two-tailed, with a P value of ≤ 0.05 indicating statistical significance.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the study population.

Our study included 76 eyes of 72 patients; 65% were female, with a mean age of 70 ± 8 years. Median (range) follow-up time was 21 (3–92) months. The duration of the follow-up was less than 6 months in 9%, 6–12 months in 18%, 12–24 months in 28%, and more than 24 months in 45%.

Table 1 Baseline characteristics of the study population

	All (*n* = 76)
Gender, n (%)	
Female	40 (65)
Male	27 (35)
Age (years), mean (SD)	70 (8)
Lens, n (%)	
Phakic	58 (76)
Pseudophakic	18 (24)
Follow-up (months), median (range)	21 (3–92)
Laterality, n (%)	
Unilateral	61 (80)
Bilateral	15 (20)
IVTS stage, n (%)	
2	17 (22)
3	22 (29)
4	37 (49)
Minimum diameter (μm), mean (SD)	447 (189)
Macular hole size, n (%)	
Small	12 (16)
Medium	16 (21)
Large	44 (58)
MHI, mean (SD)	0.6 (0.3)
Epiretinal membrane, *n* (%)	22 (29)
Preoperative logMAR BCVA, mean (SD)	1.0 (0.4)

IVTS, International Vitreomacular Traction Study; MHI, macular hole index; LogMAR, logarithm of minimal angle of resolution; BCVA, best-corrected visual acuity

MH above stage 3, according to IVTS classification, was found in 78%. The mean minimum linear diameter was 447 ± 189 μm, and the mean MHI was 0.6 ± 0.3. More than half of the eyes presented a large MH (> 400 μm).

Mean preoperative BCVA (logMAR) was 1.0 ± 0.4 (Snellen 20/200), ranging from 0.4 (Snellen 20/50) to 1.8 (count fingers). Preoperative BCVA (logMAR) was positively correlated with minimum linear diameter ($r = 0.57$, $p < 0.001$) and negatively correlated with MHI ($r = -0.32$, $p < 0{,}001$).

Surgery data

In almost all surgeries (90%), SF6 gas was used as a tamponade. PPV was combined with cataract surgery in the same surgical time in 11 of 58 phakic eyes. Eighty-one percent of the eyes remaining phakic after PPV underwent cataract surgery during follow-up. A total of 6 eyes were phakic at the end of follow-up. Median (range) time between PPV and cataract surgery was 13 (1–57) months.

The rate of preoperative complications was 9%. Four eyes developed ocular hypertension, 2 eyes had retinal tears, and 1 eye presented retinal detachment.

Main outcomes

Study results by the follow-up duration are shown in Fig. 1.

Hole closure rate

The hole closure rate was 92%, as shown in Table 2. The most common closure pattern was U-type (69%). There were no differences regarding the hole closure rate of different IVTS stages (93% for stage 2; 94% for stage 3; 90% for stage 4, $p = 0.87$).

Six holes did not close after the inverted ILM flap technique. Of these, one displayed a flat open configuration. Three cases were submitted to second MH surgery ($n = 2$ flap repositioning; $n = 1$ perifoveal radial incisions), and all of them were closed at the end of follow-up.

EZ structural analysis

After hole closure, EZ's structural defects were found in 66%, as shown in Table 3. These defects were classified as EZ atrophy in 33%, EZ disruption in 22%, and EZ thinning in 11%. Representative cases are shown in Fig. 2. Qualitative analysis of EZ defects by the follow-up duration is represented in Table 4. In this analysis, no significant differences between groups were observed.

BCVA improvement

Eighty percent had a visual acuity improvement of ≥ 0.3 units (logMAR). The mean final BCVA (logMAR) was 0.5 ± 0.4 (Snellen 20/63), ranging from 0 (Snellen 20/20) to 1.8 (count fingers). There was a significant difference between initial and final BCVA (1.0 vs. 0.5 logMAR, $p < 0.001$). After inverted ILM flap technique, the final BCVA was significantly worse in eyes with non-closed versus closed MHs (0.3 vs. 1.2 logMAR, $p = 0.02$). In those with closed MHs, final BCVA was significantly worse in eyes with EZ defects compared with eyes without EZ defects (0.55 vs. 0.26 logMAR, $p = 0.003$). In those with EZ defects, final BCVA was significantly worse in eyes with EZ atrophy than EZ disruption (0.75 vs. 0.36, $p = 0.004$) and EZ thinning (0.75 vs. 0.32, $p = 0.015$).

Predictive factors of a final BCVA < 0.30 logMAR

Binary logistic regression (Table 5) was adjusted considering the independent variables of gender, age, lens status, laterality, IVTS stage, minimum linear diameter, MHI, ERM, phacovitrectomy and preoperative BCVA. In multivariate analysis, minimum linear diameter (OR 1.01; IC 95% 1.01–1.02) independently predicted a final BCVA (logMAR) < 0.30 (Snellen 20/40).

Discussion

Inverted ILM flap technique is currently the preferred surgical technique of many vitreoretinal surgeons for the management of MHs. A detailed evaluation of anatomical and functional results of this technique is warranted since novel surgical methods are emerging.

Inverted ILM flap technique was introduced by Michalewska et al. [8], who first reported a high closure rate (98%) and good postoperative BCVA

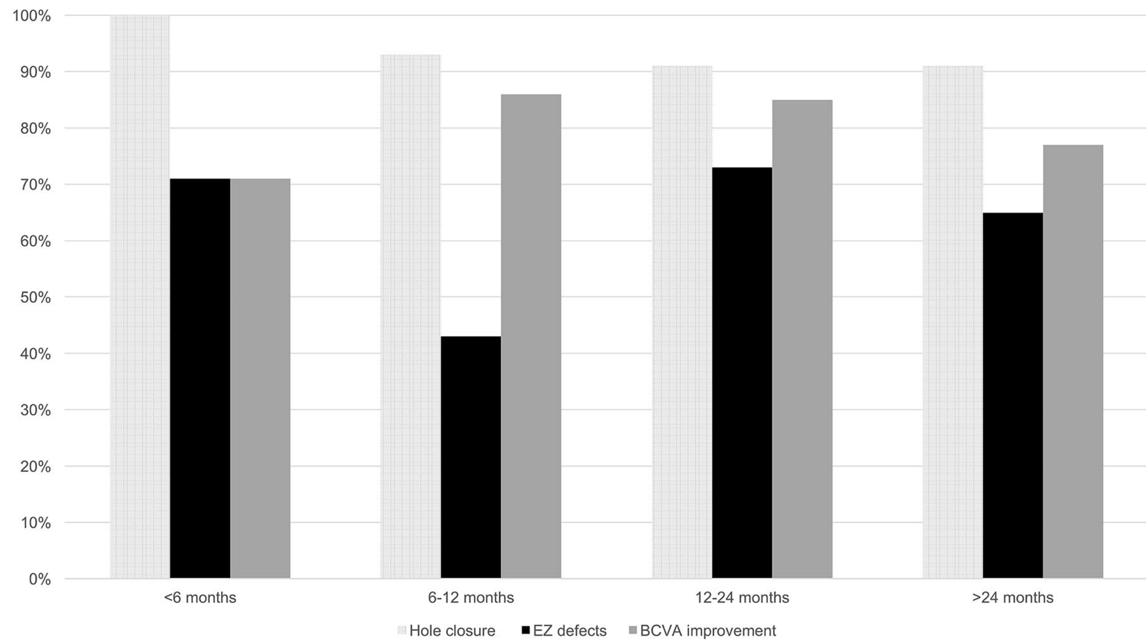

Fig. 1 Study results by the follow-up duration

Table 2 Hole closure rate and visual acuity outcomes

	All (n = 76)
Hole closure rate, n (%)	70 (92)
BCVA (logMAR) improvement $\geq$ 0.3 units, n (%)	61 (80)
Final BCVA (logMAR), mean (SD)	0.5 (0.4)
BCVA (logMAR) variation, mean (SD)	− 0.5 (0.4)

LogMAR, logarithm of minimal angle of resolution; BCVA, best-corrected visual acuity

Table 3 Characterization of the closed holes

	All (n = 70)
Closure pattern, n (%)	
U-shaped	48 (69)
V-shaped	22 (31)
*EZ changes, n (%)**	46 (66)
Thinning	8 (11)
Disruption	15 (22)
Atrophy	23 (33)

EZ, ellipsoid zone

*Two cases were unclassified

(0.28 LogMAR) in large idiopathic MHs. These results were slightly better than those described in the following studies. Yamashita et al. [20] published a high closure rate (95%) in idiopathic medium–large MHs, but a mean postoperative BCVA of 0.51 logMAR. Rizzo et al. [11] also described a 94% closure rate and a mean postoperative BCVA of 0.42 logMAR in non-myopic eyes affected by MHs. Our study found a 92% closure rate and a mean postoperative BCVA of 0.5 logMAR. Differences in the time of follow-up may explain the small drop in the hole closure rate in our study. On the other hand, visual outcomes were similar except for the study of Michalewska et al. [8], which is probably related to the inclusion criteria and smaller sample size. Despite acceptable values for final BCVA, visual acuity improvement by about 15 letters occurred in 80% of the eyes. This denotes the poor visual acuity at the

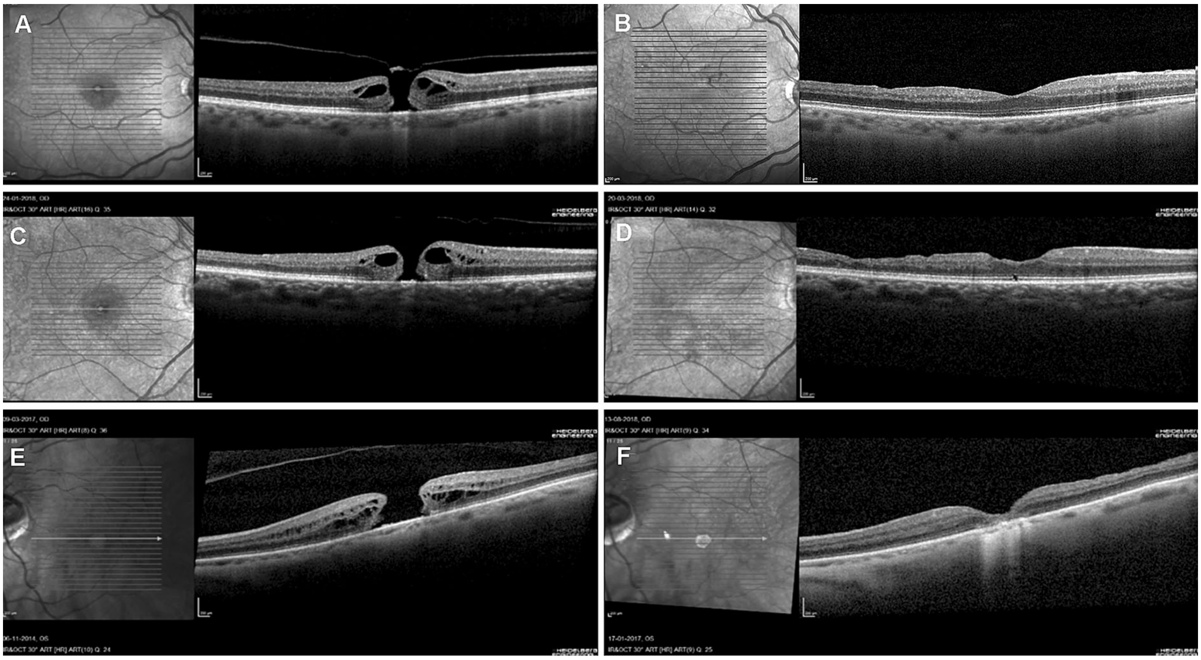

Fig. 2 Preoperative and postoperative spectral-domain optical coherence tomography (SD-OCT) images of three cases. **a, b** A 73-year-old male presented with a best-corrected visual acuity (BCVA) of 20/80 and a macular hole (MH) with a minimum linear diameter of 201 µm in the right eye. After surgery, hole closure with EZ thinning was visualized on SD-OCT and the BCVA was 20/25. **c, d** A 64-year-old female presented with a BCVA of 20/60 and a MH with a minimum linear diameter of 100 µm in the left eye. After surgery, hole closure with EZ disruption was visualized on SD-OCT and the BCVA was 20/60. **e, f** A 73-year-old female presented with a BCVA of 20/400 and a MH with a minimum linear diameter of 546 µm in the left eye. After surgery, hole closure with EZ atrophy was visualized on SD-OCT and the BCVA was counting fingers

Table 4 Qualitative analysis of EZ defects by the follow-up duration

	Duration of follow-up				p value
	< 6 months (n = 7) (%)	6–12 months (n = 13) (%)	12–24 months (n = 19) (%)	> 24 months (n = 31) (%)	
EZ disruption	29	29	13	23	p = 0.27
EZ thinning	14	14	20	4	p = 0.17
EZ atrophy	29	0	40	39	p = 0.16

EZ, ellipsoid zone

presentation of this condition. In addition, the final BCVA may be predicted by the minimum linear hole diameter. Importantly, this is one of the main predictors of the visual outcome, as demonstrated by other studies [21].

A small proportion of MHs does not close after inverted ILM flap technique. Comparable to Michalewska et al. [8], our results demonstrated that flat open appearance is rare with this technique. Initially, it was considered a type of closure associated with a worse visual prognosis [19], and the introduction of the inverted ILM flap technique was an attempt to avoid this outcome. When the inverted ILM flap technique fails, it seems reasonable to consider a second MH surgery. However, few studies have evaluated which surgical technique is most appropriate in these cases [22].

Table 5 Predictive factors of a final BCVA < 0.3 logMAR units

	Unadjusted Crude OR	95% CI	*p*-value	Covariate adjusted OR	95% IC	*p*-value
Gender						
Male	0.71	0.28–1.82	$p = 0.47$	–		
Female	1					
Age (continuous)	1.0	0.95–1.06	$p = 0.93$	–		
Lens						
Phakic	1.80	0.61–5.31	$p = 0.28$	–		
Pseudophakic	1					
Laterality						
Bilateral	1.18	0.38–3.66	$p = 0.77$	–		
Unilateral	1					
IVTS stage						
2	0.19	0.05–0.76	$p = 0.02$	1.29	0.16–10.50	$p = 0.81$
3	0.30	0.09–1.01	$p = 0.05$	0.25	0.06–1.11	$p = 0.06$
4	1			1		
Minimum diameter (continuous)	1.00	1.01–1.02	$p < 0.001$	1.01	1.01–1.02	$p = 0.02$
MHI (continuous)	0.13	0.02–0.81	$p = 0.03$	1.08	0.09–12.35	$p = 0.95$
Epiretinal membrane						
No	0.64	0.23–1.79	$p = 0.40$	–		
Yes	1					
Combined cataract surgery						
No	1.49	0.43–5.19	$p = 0.53$	–		
Yes	1					
Preoperative BCVA (continuous)	6.85	2.06–22.79	$p = 0.002$	1.42	0.28–7.06	$p = 0.66$

CI, confidence interval; OR, odds ratio; IVTS, International Vitreomacular Traction Study; MHI, macular hole index; LogMAR, logarithm of minimal angle of resolution; BCVA, best-corrected visual acuity

To better understand the regenerative process of the outer retina after inverted ILM flap technique, the recovery of the EZ structure was evaluated. Theoretically, ILM flap acts as a substrate for a secondary intention wound-healing mechanism in which a subset of Muller cells is activated and promotes the restoration of the outer retinal layers [9]. The occurrence of persistent EZ defects after inverted ILM flap technique has been previously recognized in quantitative and qualitative data-based studies. Quantitative data-based studies measured the length of EZ defects. A gradual decrease in the size of the EZ defect was noticed in a study by Vieregge et al. [23] conducted over one year after surgery. Qualitative data-based studies analyzed the appearance of the EZ line on SD-OCT. Complete recovery of the EZ line defined as a complete continuous line on SD-OCT images did not occur in any eye submitted to inverted ILM flap technique in a study of Iwasaki et al. [17], but only 14 eyes were analyzed. A similar study of Ramthoul et al. [24] ($n = 23$) identified the restoration of EZ line in 4% at 1 month, 21% at 3 months, and 52% at 6 months after PPV with inverted ILM flap. Mete et al. [25] reported a higher percentage of EZ recovery (72%) at 1 year of follow-up after 27 myopic patients undergone inverted ILM flap technique. These data suggested a slow recovery of EZ on SD-OCT for several months. As demonstrated, these studies were all characterized by a small sample size. In our study, EZ defects were detected at a significant rate (66%) of closed holes, and as expected, it was associated with a worse visual outcome. In contrast to EZ atrophy (33%), eyes with

EZ disruption (22%) and EZ thinning (11%) may display a complete recovery over time. We consider that one of our main findings is the presence of EZ atrophy in 39% of a subset of patients ($n = 31$) followed for more than 24 months. Persistent loss of external retinal layers is a disabling anatomical outcome in eyes affected by MHs with implications to visual prognosis. To the best of our knowledge, no previous studies provided similar data.

According to our findings, phakic eyes require cataract surgery shortly after PPV, and so combined surgery could be considered in these patients. Theocaris et al. [26] recommended combining phacoemulsification, intraocular lens insertion, and PPV for MH repair to improve intraoperative visualization, shorten postoperative recovery time, and decrease costs.

Our study has limitations that need to be addressed, particularly those inherent to retrospective and real-world setting studies. The follow-up time was heterogeneous among the evaluated patients, ranging between 3 and 92 months. To overcome this limitation, anatomical and functional results by the follow-up duration were also evaluated. Moreover, multiple vitreoretinal surgeons participated and may have improved skills by performing this technique over time. Only one researcher manually measured SD-OCT holes parameters. The classification of EZ defects was stipulated by the authors of the study and was not validated by previous reports. As with any qualitative analysis, subjectivity in interpreting data is difficult to avoid and, to minimize it, three retinal experts were involved in this analysis. Although these limitations, our study evaluated the anatomical success of the inverted ILM flap technique in two ways: the hole closure rate and the qualitative analysis of EZ defects in closed holes. Most previous studies defined as anatomical success the hole closure rate, but this parameter is incomplete to assess the recovery of retinal architecture. The few studies that analyzed the microstructural retinal recovery after inverted ILM flap technique was performed in a small sample of eyes. Besides, the results of this study represented the 8-year experience of a tertiary center treating MHs with this technique.

To conclude, the inverted ILM flap technique provided a hole closure rate above 90%, similar to previous studies. Although the absolute value of the final BCVA was modest, a significant visual acuity improvement was observed in 80% of the eyes. Structural defects of EZ were found in more than half of closed MHs after surgery. Evidence of postoperative retinal atrophy was associated with a worse visual outcome in the follow-up.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nisa Silva and Natália Ferreira. The first draft of the manuscript was written by Nisa Silva and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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