Scientific Research Publishing

Open Journal of Ophthalmology, 2023, 13, 143-171
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Long-Term Postoperative Perfusion Indices in Surgically Resolved Myopic Traction Maculopathy

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How to cite this paper: Quiroz-Reyes, M.A., Quiroz-Gonzalez, E.A., Quiroz-Gonzalez, M.A. and Lima-Gomez, V. (2023) Long-Term Postoperative Perfusion Indices in Surgically Resolved Myopic Traction Maculopathy. *Open Journal of Ophthalmology*, **13**, 143-171.
https://doi.org/10.4236/ojoph.2023.131014

Received: December 17, 2022
Accepted: February 25, 2023
Published: February 28, 2023

Abstract

Background: Pathological myopia can be complicated by the presence of posterior staphyloma, macular atrophy, ruptures in Bruch's membrane, pathologic choroidal neovascularization, and different degrees of myopic traction maculopathy. **Purpose:** To report the structural, functional and perfusional outcomes in patients underwent surgery for different stages of myopic traction maculopathy (MTM). **Methods:** A retrospective, consecutive, comparative, interventional, one-surgeon, case-control study was conducted in 46 eyes of 34 individuals between April 2015 and May 2021. Participants included normal emmetropic eyes (Control emmetropia, n = 25), healthy myopic eyes (Control high myopia, n = 20), and operated and structurally fully resolved myopic eyes with different stages of MTM (Surgically treated group, n = 46). Long-term postoperative functional and perfusional follow-up evaluations were performed with spectral domain-optical coherence tomography (SD-OCT) and OCT angiography. The primary outcome measure included long-term functional, structural and perfusion macular status across groups. **Results:** Forty-six eyes in 34 patients were included in the study group, with both eyes affected in 12 (26.3%) patients. The mean axial length was 29.89 ± 1.67 mm. The preoperative logMAR was 1.29 ± 0.54 and the postoperative logMAR was 0.60 ± 0.52 ($P < 0.001$), with the biggest reduction in eyes with more advanced MTM. The fellow-eye prevalence rate was 53.85%, with a mean time to surgery of 43 ± 26.77 months. The fellow-eye final VA was 0.34 ± 0.29, and the first-eye final VA was 0.80 ± 0.72 logMAR ($P < 0.05$). Majori-

ty of eyes showed abnormal macula morphology post-operation, where eyes with normal postoperative macula showed better visual improvement (P = 0.022). **Conclusion:** Compared to emmetropic and healthy myopic eyes, surgically-resolved MTM eyes generally have larger superficial foveal avascular zone area, lower vessel density, smaller choriocapillaris flow area, thinner central subfoveal thickness, and more macular defects. Eyes with stage III or IV MTM had larger deviation compared to eyes at earlier stages. Visual function change after surgery was associated with superficial foveal avascular zone area. Better functional, structural and perfusion index outcomes were observed when highly myopic eyes underwent early surgery.

Keywords

Choriocapillaris Flow Area, Deep Vascular Plexus, Foveoretinal Detachment, Myopic Foveoschisis, Foveal Avascular Zone, Myopic Macular Hole

1. Introduction

High myopia is a major cause of legal blindness in industrialized countries and its prevalence has been increasing consistently over the last few decades, predicting to affect nearly 1 billion people by 2050. Analyses of regional and temporal trends note pronounced rises in incidence of myopia across the world, reaching up to 80% - 90% of the population in East and Southeast Asia (up to 20% with high myopia) [1]. In the United States, it is estimated to affect nearly 2% of the general population between 12 and 54 years of age, placing increased emphasis on the development of prevention and treatment approaches [2] that could prevent vision loss and blindness due to pathological myopia (PM). Estimates indicate that it is the fifth leading cause of blindness in Japan and second in China (in people over the age of 40) [3].

High myopia (spherical equivalent of -6.0 diopters or an axial length greater than 26.5 mm) is associated with a number of pathological macular changes. These include retinal atrophy, ruptures in Bruch's membrane, and sclerotic thinning. PM, characterized by the presence of myopic lesions in the posterior fundus and a frequent posterior staphyloma (PS) [4], is associated with the development of myopic traction maculopathy (MTM) in approximately 30% of patients. Contrary to earlier hypotheses suggesting separation of inner and outer retina layers as the pathological mechanism, MF has been found to result from the tractional elongation of the Henle nerve fiber layer in eyes with PM [5] [6]. Early stage MTM is accompanied by myopic foveoschisis (MF) that leads to the thickening of the retina and is more common in women [7] [8].

Pathological findings in posterior segments of eyes with high myopia can be attributed to scleral alterations, including scleral thinning and localized ectasia, resulting from degradation of individual collagen fibers [9] [10]. MF is a recently coined term, first used by Panozzo and Mercanti [7] to describe the pattern of

subtle macular changes observed using optical coherence tomography (OCT). These changes implicate epiretinal membrane (ERM), vitreomacular traction (VMT), macular or foveal retinoschisis, retinal thickening, a lamellar or partial-thickness macular hole, and a full-thickness myopic macular hole (MH) with or without retinal detachment and PS. The thinning and the deformation of the sclera lead to axial elongation that is hypothesized to be the key pathophysiological mechanism behind foveomacular retinoschisis that exacerbates pre-existing VMT. The VMTs are considered to be the sources of traction-related vitreoretinal interface abnormalities, such as ERMs, posterior cortex hyaloid remnants, and retinal vessel rigidity [5]. In addition, enhanced-depth OCT imaging has revealed choroidal thinning in the macular region to be a consequence of age-related degenerative changes [11] [12].

The Clinical MTM Staging recently proposed by Parolini *et al.* [13] [14] recognizes four MTM retinal stages (1 through 4) and three foveal stages (a through c). Early MTM is observed at Stages 1 and 2; retinal detachment is observed at Stages 3 and 4. Progression through the MTM stages is associated with vision loss as indexed by the reduction in best-corrected visual acuity (BVCA) [14]. Accurate pathological staging of MTM is pivotal for informed decision making regarding the timing of surgical treatment of the affected eye as well as the fellow eye [15]. Early stage MTM and the presence of MF are observed in between 9 and 34% of patients with PM [7] [16] [17]. Progression to later stages in highly myopic eyes with macular or foveal retinoschisis and foveal retinal detachment (FRD) ultimately results in the development of macular holes [18] [19] [20].

Although research has generally suggested long-term stability of early-stage MTM patients, some inevitably progress to FRD/MH and associated visual impairments [5], likely due to substantial tractional forces [21]. The proposed mechanisms for the pathogenesis of foveal schisis include both axial traction from the progressive elongation of eyeball and the subsequent stretching force affecting the posterior retina. These degenerative and deformative findings are present within the context of PS [22] [23]. It should be noted that pre-macular vitreoschisis cavity with outward tangential traction may be secondary to the rigidity of the internal limiting membrane (ILM) and retinal vessels.

Pars plana vitrectomy (PPV) with modified fovea sparing ILM or without ILM peeling and tamponade with silicone oil or gas are currently available treatments for MTM. Macular buckling has also been tried in this population of patients with favorable results [15] [24] [25] [26] [27]. The identification of early stage MTM is a major factor guiding management strategy and treatment decision-making. Visual recovery is achieved postvitrectomy by eliminating vitreoretinal traction; however, additional interventions may sometimes be needed to improve other functional and anatomical parameters.

The optimal timing of macular surgery during different stages of MTM continues to be a controversial topic [11] [12]. Varying surgical indications have

been associated with variable anatomical and functional results [8] [25] [28] [29]. Recent developments in qualitative and quantitative perfusional evaluation of vessel density (VD) and choriocapillaris flow patterns at the macular level present a unique opportunity and instruments to fine-tune the approach to the detection, evaluation, staging, and management of different macular pathologies [30] [31] [32] [33]. Thus, the present study aimed to compare the quantitative macular microcirculation indices in the control emmetropia, control high myopia (**Figure 1**), and operated eyes with MTM. Surgical cases were selected as illustrated in **Table 1** (different stages of MTM resolved completely after macular surgery) to satisfy strict criteria designed to minimize the effects of possible confounding variables.

2. Materials and Methods

This study adhered to the guidelines set by the Declaration of Helsinki and was authorized by the study institution's ethics and teaching councils. No reference number is required or provided for retrospective studies by the Institution. The study was a retrospective analysis of data from a sample of eyes obtained from the Retina Specialists Unit at Oftalmologia Integral ABC Institution in Mexico City. All study participants provided written informed consent to be included. The IRB of the facility approved the study and enabled secure access to the medical records of the patients who provided written informed consent for use of their data for research purposes. Data are available from the Imageology Laboratory upon request, and at the following link: https://www.dropbox.com/sh/dx0ig568houbkwg/AACj-AvLmW9XOC2pL8n7_NQka?dl=0.

According with the study design three groups of eyes were included as follows: 25 normal eyes (control emmetropic group) with no previous disease history, BCVA of 20/20, normal intraocular pressure in the range of 10 to 21 mmHG and exhibiting no abnormalities on dilated fundus examination and OCT evaluation. 20 normal myopic eyes (control highly myopic group) with spherical equivalent refractive error of >6.0 diopter or axial length > 26.5 and no abnormalities on fundus examination or OCT structural evaluation were also included. The surgical treatment group (surgical group) included only eyes with PS from a series of consecutively enrolled patients who underwent vitrectomy with successful and uncomplicated macular surgery. MTM staging was performed using spectral-domain OCT (SD-OCT) findings. Symptomatic MTM was surgically resolved using a range of ILM techniques as outlined by Parolini *et al* [14]. All patients in the surgical group were evaluated on the following schedule using a standardized protocol: monthly for six months followed by an examination every six months until the last follow-up visit; all patients had their operations performed by the same surgeon. Study groups were matched on age and biological sex, as well as on study and follow-up durations.

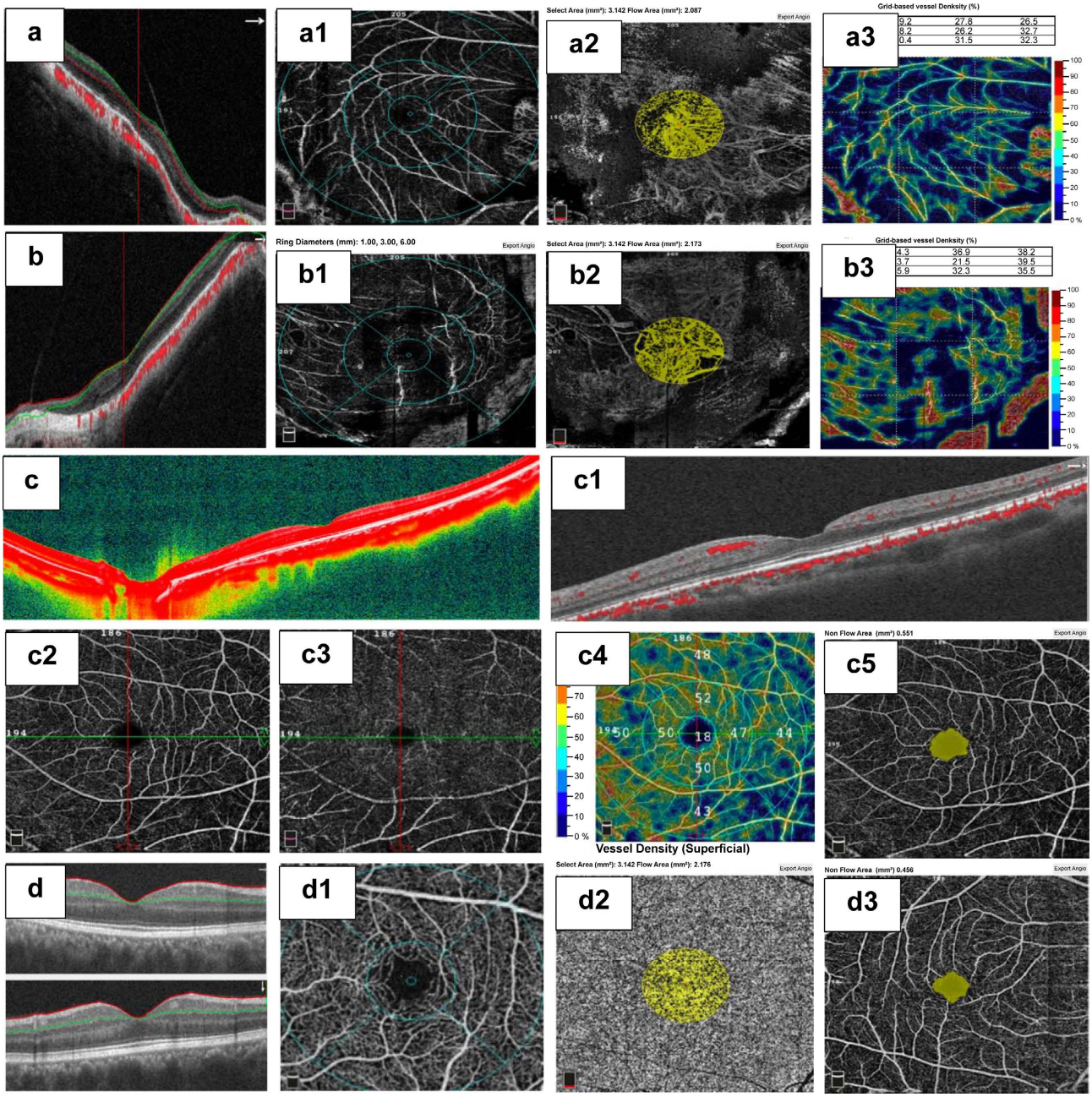

Figure 1. Normal control groups. (a) Horizontal b scan of a highly myopic eye with automated red and green segmentation lines, the posterior hyaloid membrane is still attached. (a1) image depicts a quantitative deep vascular plexus (DVP) slab with the ETDRS-like sectors grid overlay. (a2) image depicts a normal quantified area of choroidal flow with an irregular but normal perfusion index at the selected subfoveal choriocapillaris. (a3) The color overlays on the OCTA angiography image indicate a normal vessel density value in the key to the right. (b) Horizontal segmented SD-OCT in a highly myopic eye with normal biomarkers. (b1) image shows slab of the superficial vascular plexus (SVP). (b2) image depicts a normal area of choroidal flow at the subfoveal selected area. (b3) image indicates a normal vessel density value in the key to the right. (c) Enhanced HD Line 12 mm horizontal B scan designed to depict more detail in the vitreoretinal interface with brighter colors in a normal eye. (c1) corresponding horizontal B scan with red dots indicate intraretinal and choriocapillaris vascular flow. (c2) and (c3) corresponding normal SVP and DVP. (c4) The color overlays on the OCTA angiography image indicate a normal vessel density value in the key to the left. (c5) image depicts a normal foveal avascular zone (FAZ) of 0.551 mm^2. (d) image shows a crossline automated segmented green and red SD-OCT with normal biomarkers. (d1) image depicts a normal SVP slab with a normal well-defined pericapillary network. (d2) image shows a normal choriocapillaris flow area. (d3) image shows a normal FAZ of 0.456 mm^2.

Table 1. Summary of study groups and inclusion criteria.

Study group	Inclusion criteria
Control emmetropia (n = 25)	No previous disease history, BCVA ≥ 20/20, intraocular pressure ≥ 10 to ≤21 mmHg, no abnormalities on dilated fundus examination and OCT scan
Control high myopia (n = 20)	Spherical equivalent refractive error of >−6.0 diopters or axial length > 26.5 mm
Surgical treatment group (n = 46)	Stage 1-Eyes exhibiting Myopic Foveoschisis Stage 2-Eyes with evidence of Foveoetinal Detachment Stage 3-Eyes with evidence of a partial-or full-thickness macular hole Stage 4-Eyes with posterior pole rhegmatogenous retinal detachment associated with an macular hole

BCVA: best-corrected visual acuity, OCT: optical coherence tomography.

Patients with the following characteristics were excluded: Eyes with patchy foveal-affected chorioretinal atrophy, neovascularization according to the ATN [34], previous record of surgical complications, severe proliferative vitreoretinopathy associated with recurring MHRD, the existence of active glaucoma. Similarly, patients with critical complications (e.g., endophthalmitis) were excluded. Eyes that received intravitreal injections or laser photocoagulation during the study were not analyzed in this study. In addition, subjects who were lost to follow-up were also excluded. Overall, 46 eyes that met the inclusion and exclusion criteria were selected and classified based on the preoperative MTM stage and the surgical procedure used to correct this structural condition. **Table 1** describes the study group composition and inclusion criteria.

2.1. Ocular Examinations

Ophthalmic evaluations and preoperative assessments administered in all patients included BCVA, Amsler grid test, slit lamp biomicroscopic examination, and detailed fundus evaluation using a panfundoscopic contact lens and indirect ophthalmoscopy. Cross-sectional images of the macular region were acquired along the horizontal plane through the foveal center using a SD-OCT (RTVue-XR platform SD-OCT; Optovue, Inc., Fremont, CA, USA), and axial lengths were measured using partial coherence laser interferometry (Zeiss IOL Master 700; Carl Zeiss Meditec AG, Oberkochen, Germany). PS presence was confirmed using B-scan ultrasonography (US A and B, Quantel Medical, Du Bois Loli, Auvergne, France) and indirect ophthalmoscopy.

Postoperative microstructural evaluations were performed using SD-OCT as described above. Study methods including details about procedures for BCVA evaluation, postoperative perfusional, and quantitative vessel VD, choroidal flow assessment, imaging, and data quality control and assurance are presented elsewhere in a recently published case series by Quiroz-Reyes M *et al.* [35].

The foveal avascular zone (FAZ) area in the SVP slab was evaluated by ana-

lyzing en face images saved as PNG files in the AngioVue system. Each FAZ area was automatically outlined following AngioAnalytics with angiometrics in the AngioVue software system to facilitate the measurements. Only scans with an SSI of >46 were included. Projection artifacts were automatically excluded with digital outlining of the FAZ in the SVP. The superficial FAZ area was quantitatively calculated. A built-in tool in the AngioVue system measured the VD [36] [37], and a quantitative evaluation of the SVP and DVP was then automatically generated. In built automated software processes the image information generating sets of VD and flow index (perfusion indices) for four en-face sections of the retina. We defined perfusion indices represented by VD as the proportion of the vessels area with blood flow over the total measured area. We defined whole-macula VD and choriocapillaris flow area (CFA) as density values within a 3 mm × 3 mm square and a 1-mm-diameter circle automatically selected in the foveal area, respectively.

2.2. Surgical Procedures

All eyes in the surgical treatment group underwent a standard 23-or 25-gauge three-port pars plana vitrectomy under local anesthesia plus sedation. Core vitrectomy and triamcinolone acetonide-assisted (Kenalog 40 mg/mL, Bristol-Myers, New York, NY) removal of cortical vitreous from the surface of the retina was performed using a silicone-tipped cannula and active suction. Special care was exerted to obtain a free and mobile posterior hyaloid membrane. Surgical macular evaluation and revision was performed in using trypan blue 0.15% ophthalmic solution (Membrane Blue, Dutch Ophthalmic, USA). The study and surgeon utilized modified ILM peeling techniques, including the foveal-sparing ILM, the inverted-flap ILM peeling and free-autologous ILM transplantation. The study followed the detailed protocols previously described by Quiroz-Reyes MA, *et al.* [32], including gauge vitrectomy cut and suction instrument, ILM peeling technique, special procedures for phakic eyes, and other considerations.

2.3. Outcome Measures

Functional visual acuity outcomes were measured as the logarithm of the minimum angle of resolution (logMAR). Surgical success was defined as a significant reduction/disappearance of MF; clinically and tomographically resolved FRD; closure of the retinal hole or macula/retina reattachment status before the final visit (regardless of the number of procedures). SD-OCT findings were obtained pre-operatively and at the last follow-up evaluation to perform microstructural comparisons among study groups. Postoperative macular perfusion indices were obtained, processed, and statistically correlated.

2.4. Statistical Analysis

Data were entered and aggregated in Microsoft Excel. Statistical analysis and visualization were performed using GraphPad Prism version 8.2.1 and SPSS ver-

sion 28. Distribution normality was assessed empirically and guided the selection of the statistical tests. One-Way Analysis of Variance (ANOVA) was employed for parametric analysis and the Kruskal-Wallis test was used for non-parametric analysis. Dunnett's test was used for post-hoc analysis. Spearman rank correlation test was used to interrogate the association between perfusion indices and final visual outcomes. Changes from Pre-op to Post-op BCVA (logMAR) values were analyzed using the Wilcoxon matched signed-rank test. We used the final postoperative BCVA to analyze differences in visual outcomes between stages, types of tamponade and surgical variants. P-values below nominal Type I error rate of 5% ($P < 0.05$) were considered statistically significant.

3. Results

3.1. General Outcome

In the Stage 1 or myopic foveoschisis (MF) group, macular hole was evident in 1/5 eyes post-surgery (20%). The mean postoperative BCVA was significantly better when compared with the preoperative BCVA (Figure 2). In Stage 2 or Foveoretinal detachment (FRD) group, the median preoperative and postoperative BCVAs in this group were 1.00 (0.60 to 1.30) logMAR and 0.30 (0.09 to 1.00) logMAR, respectively, which differed significantly ($P < 0.001$). In Stage 3 or myopic macular hole (MH) group, the median preoperative and postoperative BCVAs in this group were 1.15 (0.54 to 1.30) logMAR, and 0.49 (0.09 to 1.00) logMAR, respectively, which differed significantly ($P < 0.001$). In the Stage 4 macular hole retinal detachment (MHRD) group, the median preoperative and postoperative BCVAs in this group were 1.15 (0.54 to 1.30) logMAR, and 0.60 (0.30 to 1.00) logMAR, respectively, which differed significantly ($P < 0.001$). Table 2 summarizes the demographic and preoperative clinical characteristics of the included patients.

The postoperative follow-up period differed across stages of the disease. The Stage 1 disease follow-up period (13 months, 6 - 58; median, range) tended to be shorter than more advanced stages ($P > 0.05$) (Table 2). The postoperative follow-up period was longest in Stage 4 disease (40 months, 6 - 67; median, range). Across all surgical eyes, the mean (SD) preoperative evolution of MTM was 11.34 (7.12) months, the postoperative time for FRD resolution was 5.48 (2.22) weeks, and the postoperative follow-up time was 23.96 (15.04) months. Diffuse chorioretinal atrophy with secondary macular atrophy was the most common complication across all stages of the disease. Full-thickness MH development was the most common complication observed in the MF/FRD stages (12.9%) followed by rhegmatogenous retinal detachment (5%); three eyes (6.5%) showed refractory FRD after surgery; and six eyes (13.1%) showed an open but sealed MH at the end of follow-up (Table 3).

3.2. Structural and Perfusion Findings among Groups

A microstructural analysis of the SD-OCT findings was conducted based on the

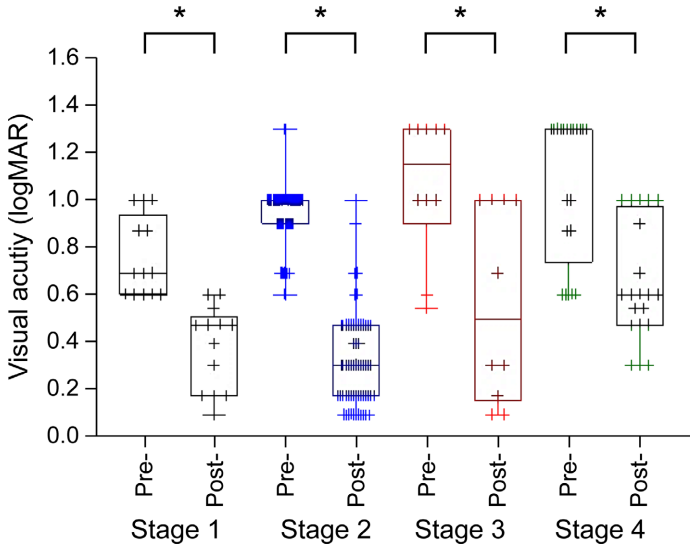

Figure 2. The postoperative BCVA improved significantly in all stages of the disease ($P < 0.001$). The graphs show the median with range for each individual stage of the disease. The postoperative BCVA in the surgically treated groups remained poorer than that in the emmetropic control groups ($P < 0.0001$). Stage two disease resulted in a better BCVA than the other three stages ($P < 0.0001$).

Table 2. Patients' demographic data and preoperative clinical characteristics.

Study group	Female (%)	Median age (min to max, years)	Preoperative median BCVA (min to max, logMAR)	Axial length (mean ± SD, mm)	Postoperative follow-up months (median, range)
Control emmetropic group (n = 25)	76	52 (22 to 66)	0.00 (−0.12 to 0.09)	20.53 ± 0.09	-
Control myopic group (n = 20)	70	60 (48 to 70)	0.00 (0.00 to 0.09)	29.45 ± 1.49	-
Surgical treatment group (N=46)					
Stage 1 (n = 5)	84.6	59 (44 to 70)	0.69 (0.60 to 1.00)	30.54 ± 1.51	13 (6 - 58)
Stage 2 (n = 26)	75.4	59 (43 to 76)	1.00 (0.60 To 1.30)	29.38 ± 1.64	27 (6 - 67)
Stage 3 (n = 4)	90	61 (46 to 70)	1.15 (0.54 to 1.30)	30.10 ± 1.33	15.50 (6 - 62)
Stage 4 (n = 11)	71.4	58 (43 to 82)	1.30 (0.60 to 1.30)	29.94 ± 1.71	40 (6 - 67)

BCVA: best-corrected visual acuity, logMAR: logarithm of the minimum angle of resolution; SD: standard deviation.

International Nomenclature for Optical Coherence Tomography (IN•OCT) Panel [38]. The results of the analyses of the relationship between visual outcomes and functional, structural and perfusional indices across treatment groups and different stages of the diseases are summarized in Table 4. The quantitative evaluation of macular perfusion and central subfoveal thickness (CSFT) across study groups is depicted in Table 4. The postoperative BCVA in the surgically treated groups remained poorer than that in the emmetropic control groups ($P < 0.0001$) (Table 4). Stage 2 disease resulted in a better BCVA than the other three stages ($P < 0.0001$). Briefly, the perfusion analysis showed that the superficial FAZ area in the control emmetropic groups was significantly smaller than that

Table 3. Quantitative evaluation of macular perfusion and central subfoveal thickness across study groups.

Study groups	Superficial FAZ area (mm^2, mean ± SD)	Superficial foveal VD (%, mean ± SD)	Deep foveal VD (%, mean ± SD)	Superficial parafoveal VD (%, mean ± SD)	Deep parafoveal VD (%, mean ± SD)	Superficial whole macula VD (%, mean ± SD)	Deep whole macula VD (%, mean ± SD)	Choriocapillaris flow area (mm^2, mean ± SD)	CSFT (μm, mean ± SD)	Post-Op Median BCVA (Min to max, logMAR)
Control emmetropic (n = 25)	0.33 ± 0.04	27.17 ± 3.40	31.39 ± 3.06	58.76 ± 3.03	59.17 ± 2.60	56.93 ± 4.27	58.50 ± 3.66	2.51 ± 0.24	246.40 ± 21.12	0.00 (−0.12 to 0.09)
Control high myopia (n = 20)	0.64 ± 0.12*	27.57 ± 3.91	32.11 ± 4.27	55.24 ± 2.56*	54.98 ± 2.051*	46.35 ± 3.36*	48.55 ± 2.65*	2.25 ± 0.22	264.9 ± 37.91	0.00 (0.00 to 0.09)
Stage 1 (n = 5)	0.74 ± 0.29*	28.53 ± 5.47	31.13 ± 4.56	49.66 ± 6.79*	51.53 ± 6.28*	48.81 ± 4.84*	50.13 ± 5.47*	1.90 ± 0.12*	228.60 ± 48.54	0.47 (0.09 to 0.60)*
Stage 2 (n = 26)	0.77 ± 0.25*	28.95 ± 5.72	31.45 ± 5.12	49.71 ± 4.58*	50.83 ± 4.72*	50.26 ± 3.97*	50.37 ± 4.02*	1.85 ± 0.28*	208.70 ± 29.97*	0.30 (0.09 to 1.00)*
Stage 3 (n = 4)	1.28 ± 0.35*	21.27 ± 4.35*	25.51 ± 4.17*	37.14 ± 4.61*	39.58 ± 4.30*	40.29 ± 4.21*	41.46 ± 3.92*	1.35 ± 0.18*	194.70 ± 10.86*	0.49 (0.09 to 1.00)*
Stage 4 (n = 11)	1.66 ± 0.40*	22.64 ± 4.13*	23.71 ± 3.50	27.91 ± 4.39*	29.81 ± 4.79*	31.41 ± 4.09*	33.69 ± 3.43*	1.35 ± 0.22*	214.80 ± 22.01*	0.60 (0.30 to 1.00)*
(p values)	Comparison with control emmetropic	0.0001	0.0058	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

*Indicates the groups where data differed significantly (P < 0.05) from the control emmetropic group. The BCVA in the control emmetropic and control high myopia groups was used for comparison with post-Op BCVA in the surgical groups. Abbreviations: FAZ: foveal avascular zone, VD: vessel density, CSFT: central subfoveal thickness, logMAR: logarithm of the minimum angle of resolution, SD: Standard Deviation.

Table 4. The correlation of final visual outcome with the perfusion indices (vessel density and flow index). Data indicate p values and Spearman correlation co-efficient.

Study groups	Superficial FAZ area, p value (r coefficient)	Superficial foveal VD, p value (r coefficient)	Deep foveal VD, p value (r coefficient)	Superficial parafoveal VD, p value (r coefficient)	Deep parafoveal VD, p value (r coefficient)	Superficial whole macula VD, p value (r coefficient)	Deep whole macula VD, p value (r coefficient)	Choriocapillaris flow area, p value (r coefficient)	CSFT, p value (r coefficient)
Stage 1 (n = 5)	0.12 (−0.55)	0.55 (0.24)	0.96 (0.03)	0.89 (0.06)	0.75 (0.13)	0.96 (−0.03)	0.50 (−0.25)	0.47 (0.29)	0.68 (0.17)
Stage 2 (n = 26)	0.77 (0.03)	0.78 (−0.03)	0.76 (−0.04)	0.65 (0.06)	0.58 (0.07)	0.74 (−0.04)	0.96 (0.007)	0.91 (0.01)	0.29 (−0.14)
Stage 3 (n = 4)	0.39 (−0.32)	0.59 (0.20)	0.73 (0.13)	0.76 (−0.11)	0.73 (−0.13)	0.73 (−0.13)	0.64 (−0.17)	**0.04* (0.69)**	0.71 (−0.14)
Stage 4 (n = 11)	0.50 (0.16)	**0.01* (0.56)**	0.07 (0.42)	0.75 (−0.07)	0.92 (0.02)	0.85 (−0.04)	0.63 (0.11)	0.85 (−0.04)	0.48 (−0.17)

*Indicates the groups where a positive correlation to the final BCVA was observed (P < 0.05). Abbreviations: FAZ: foveal avascular zone, VD: vessel density, CSFT: central subfoveal thickness, SD: Standard Deviation.

in all other groups (P < 0.0001). The superficial foveal VD in the emmetropic group differed only from stage 3 to stage 4 of the disease (P < 0.0001). Significant

differences were only observed for deep foveal VD between Stage 3 disease and emmetropic eyes (P = 0.0058). Similarly, the CFA was significantly larger in the emmetropic group (P < 0.0001).

Decreased superficial foveal VD correlated with poor visual outcome in Stage 4 disease (P = 0.014). Similarly, a smaller CFA was associated with poorer visual outcome (P = 0.048) in Stage 3 disease. Additionally, CSFT tended to correlate negatively with the final BCVA (Table 4). Preoperative and final BCVAs by stage, group and surgical procedures are compared in Table 5, which shows that final visual acuities were significantly better across all the study variables

Multivariate regression analysis was conducted to identify putative biomarkers for functional BCVA, anatomical CSFT, and structural defects in EZ and ELM layers. Analysis results showed that BCVA was positively correlated with the CFA (analysis done with BCVA converted to logMAR scale, which showed a negative correlation with the CFA (Table S1). In the surgical group, superficial FAZ area was found to positively correlate with postoperative change in BCVA (Table S2). Analysis also revealed that anatomical CSFT was positively correlated with superficial foveal VD (Table S3). The presence of the EZ defect was found to be positively correlated with superficial whole macula VD and negatively correlated with deep whole macula VD (Table S4). Lastly, the presence of ELM defect was found to be negatively correlated with deep parafoveal VD (Table S4). It is worth noting that none of the p-values were very small, with the smallest being P = 0.006 in the analysis of ELM defect, study sample size constrained statistical power in these analyses. The correlation analysis with ELM defects is shown in supplemental Table S5.

Figures 3-6 illustrate some representative surgical cases.

4. Discussion

MTM is a complex disease that is frequently observed in eyes with PM. Our current understanding of its pathophysiology, etiology, clinical course, and the evidence base for data-driven intervention strategies are limited. Likewise, existing

Table 5. Comparison between preoperative and final BCVA by stage, group and surgical procedures (logMAR, median, interquartile range).

Variable	Preoperative	Final	P*
First eye	1.00 (0.95 - 1.45)	0.48 (0.30 - 0.70)	<0.001
Fellow Eye	1.00 (0.90 - 1.30)	0.18 (0.12 - 0.53)	<0.001
Tamponade			
Gas	1.00 (0.90 - 1.30)	0.30 (0.16 - 0.54)	<0.001
Silicon	1.60 (1.00 - 2.30)	0.70 (0.48 - 0.70)	<0.001
Single surgery			
Yes	1.00 (0.90 - 1.30)	0.30 (0.18 - 0.62)	<0.001
No	1.60 (1.00 - 2.30)	0.70 (0.53 - 1.08)	<0.001

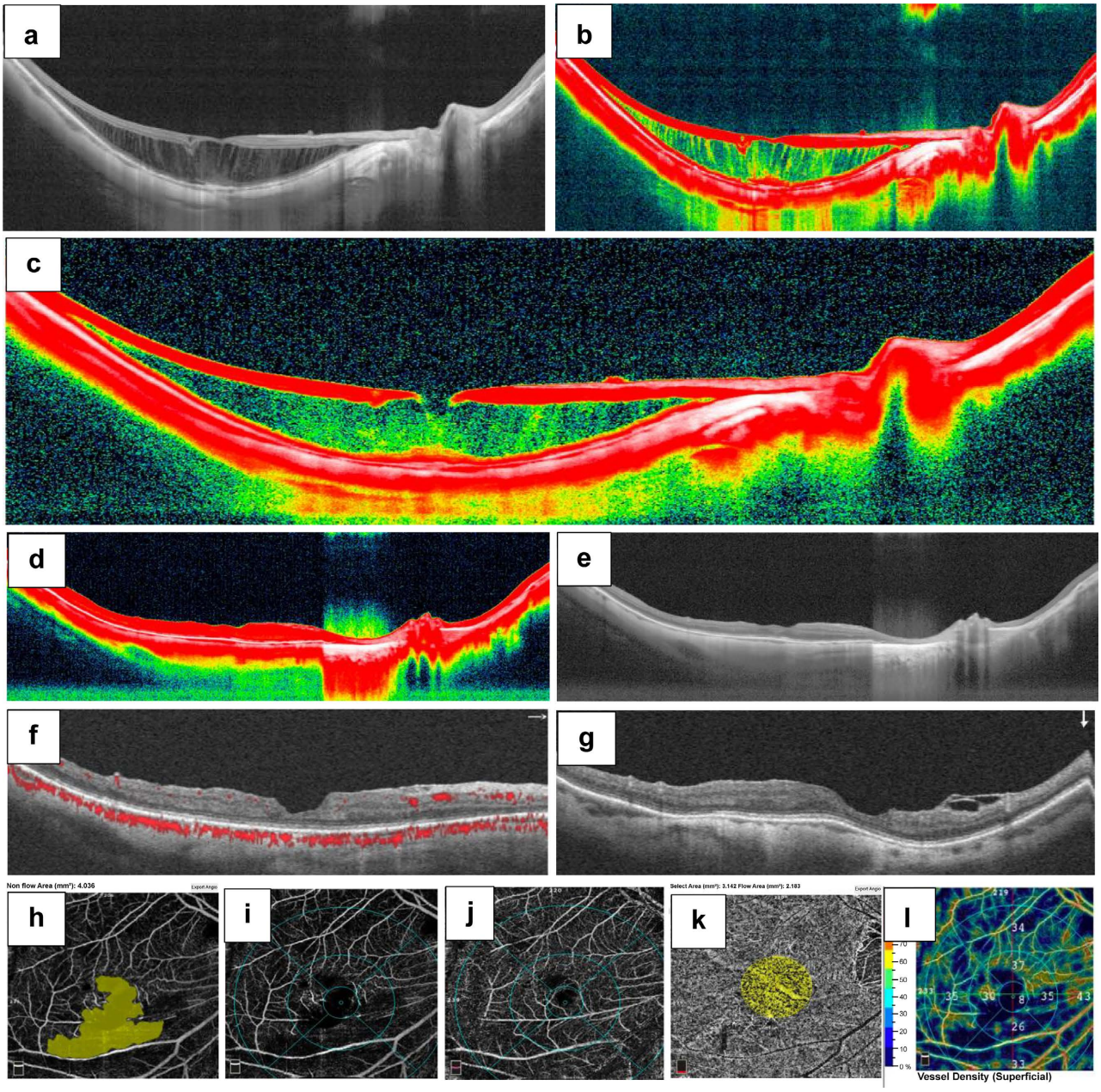

Figure 3. *Surgical case 1.* A 39-year-old symptomatic woman complained of metamorphopsia and progressive visual loss in her right eye over seven months. Her preoperative right eye visual acuity was 20/160 (logMAR 0.90) with a refractive defect of −20.00 + 2.00 × 170 and an applanation ocular tension of 11 mmHg. The right eye had an axial length of 28.71 mm with PS. (a) Image showing a high-definition 12 mm horizontal B scan with schisis-like macular thickening and tractional elongation of the Henle nerve fiber layer. (b) Image corresponding to HD in brighter color. (c) Image of the corresponding eye two months later with dehiscence of the thin fovea. The patient underwent macular surgery with a modified foveal-sparing ILM-peeling technique using BBG dye as an adjuvant to precisely identify the ILM and complete a modified foveal-sparing ILM technique and a nonexpandable 15% perfluoropropane gas mixture. (d) SVP with an abnormal perfusion index. (d) brighter color B scan of the foveomacular region that remained attached after 33 months with a final BCVA of 20/40 (logMAR 0.30). (e) and (f) Images showing horizontal B scans with an irregular foveal profile, well-defined ellipsoid zone and external limiting membrane line, the red dots corresponds to the choriocapillaris flow. (g) HD vertical B scan with some posterior hyaloid remnants superior to the fovea. (h) postoperative enlarged and irregular FAZ. (i) and (j) lower-than-normal perfusion indices on the SVP an DVP respectively. (k) The choriocapillaris flow area was considered within range with a VD perfusion index value lower than the mean. (l) Superficial vessel density with perfusion defects inferotemporal to the FAZ.

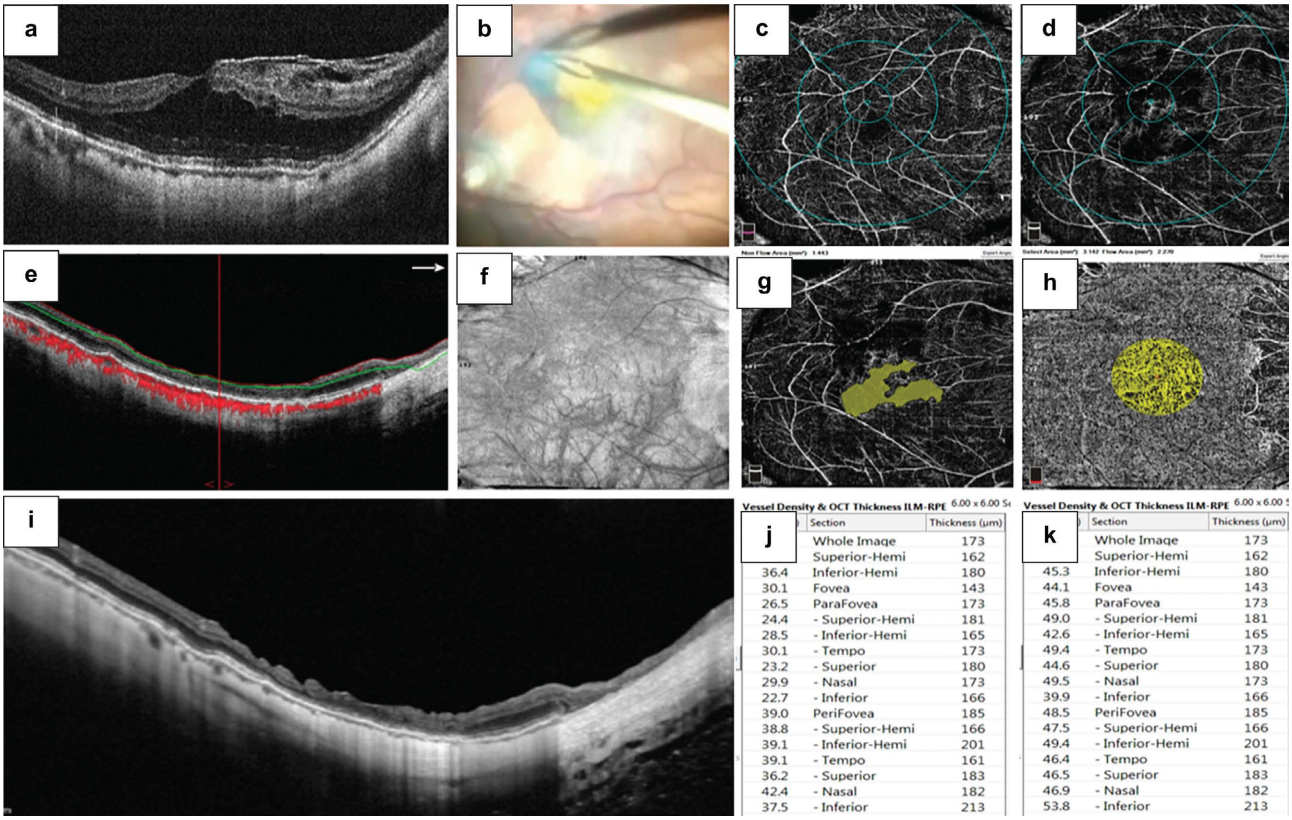

Figure 4. *Surgical case 2*. A 62-year-old symptomatic woman presented with aggravating metamorphopsia, a progressive drop in central vision, and high myopia. She had PS in both eyes; the right eye with an axial length of 29.12 mm underwent surgery because of a 9-month history of symptomatic myopic FRD. (a) Image depicting a foveo retinal detachment (FRD), internal and external schisis-like retina thickening with central subretinal fluid and epiretinal membrane. The preoperative BCVA was 20/200 (logMAR 01.00); this eye underwent a three-port 25-G pars plana vitrectomy and nonfoveal ILM peeling with the foveal-sparing technique (image b), and fluid-air-gas exchange was performed with 15% C_3F_8 tamponade, the eye showed a postoperative BCVA of 20/25 (logMAR 0.10). (c) and (d) Images depicting the deep and superficial vascular plexus with lower-than-mean perfusion indices. (e) Image depicting an automated red and green segmentation line horizontal B scan with diffuse thinning of the superficial retinal layers and with no evidence of recurrent FRD or macular hole, the red dots represent choroidal flow. (f) En face image depicting the thin retinal pigment epithelium. (g) Image depicting an irregular and enlarged FAZ of 1.443 mm^2. (h) Image showing a normal choriocapillaris flow of 2.270 mm^2. (i) HD SS-OCT image 9 mm horizontal b scan depicting some postoperative DONFL defects, with no evidence of posterior hyaloid remnants detected. (j) and (k) Correlated perfusion index values and macular thickness at the different superficial and deep submacular regions showing numbers below the mean value.

surgical approaches to the treatment of MTM as well as its complications are constrained by lack of data from prospective trials and the small number of reported case series published to date. Vitreomacular traction is likely the primary pathophysiological mechanism behind the development of MTM; yet, little is known about other possible mechanisms implicated in its etiology, vascular and perfusional alterations associated with VD in particular. Correspondingly, vitrectomy and its variant techniques with or without ILM removal and the use of different types of tamponades remain the most appropriate and recommended surgical techniques for the treatment of MTM [17].

The main objective of the present study was to conduct a formal investigation of quantitative long-term perfusion indices (VD and flow index) at the macular

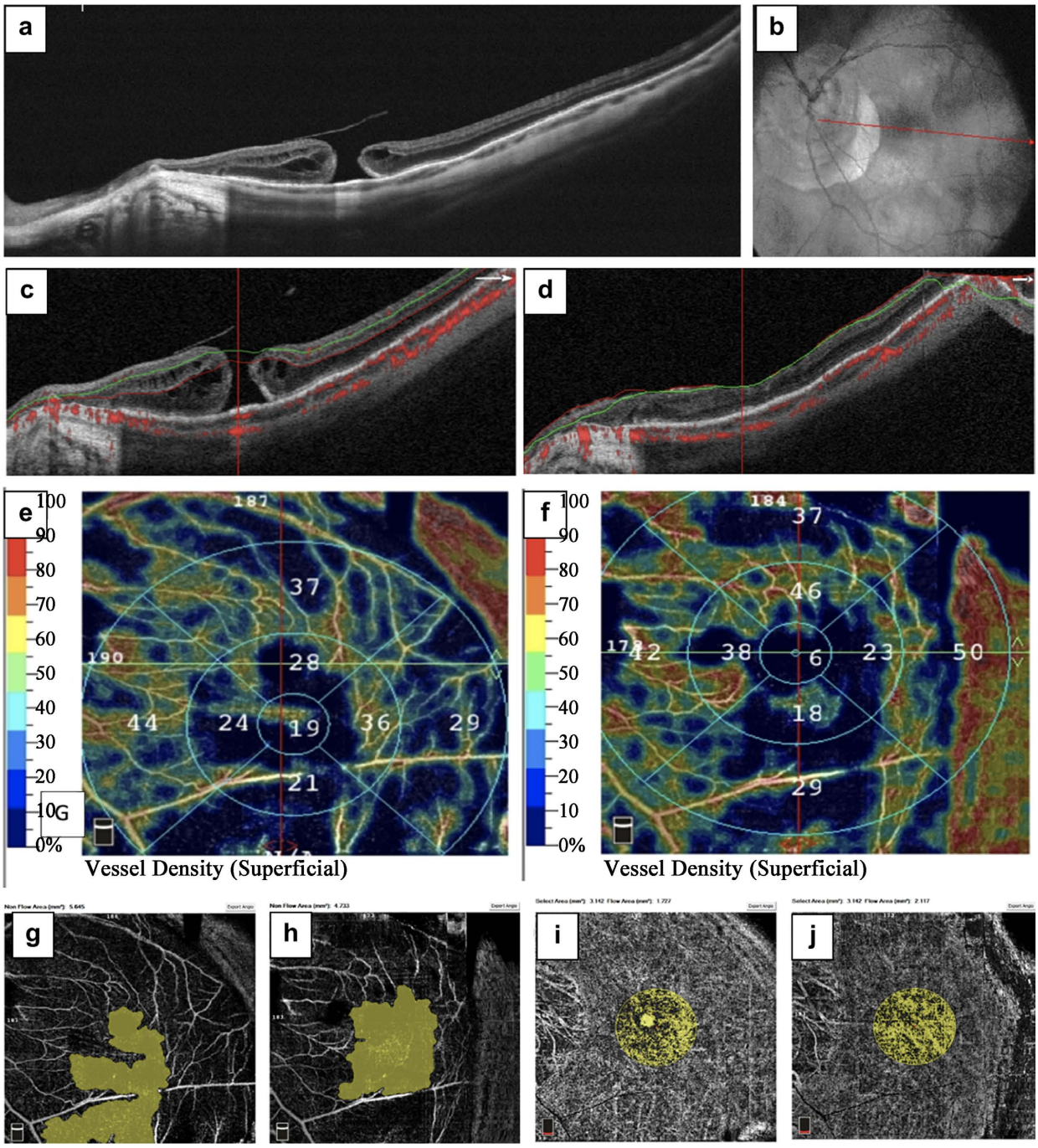

Figure 5. *Surgical case 3*. A 47-year-old symptomatic man complained of progressive visual loss and distortion in his left eye over eleven months. His BCVA at the first examination was 20/200 (logMAR 1.00) with a refractive defect of −22 + 3.00 × 20 and applanation ocular tension of 14 mmHg. The axial length was 31.21 mm with PS (a) Image of a high-definition 12 mm horizontal B scan in this case of a full-thickness macular hole with persistent vitreoretinal traction at the nasal edge. (b) En face image of the posterior pole of this case. Peripapillary chorioretinal atrophy is depicted along with diffuse retinal pigment epithelium thinning. (c) Red and green segmentation lines horizontal cross-sectional b scan depicting a full-thickness MH and persistent vitreoretinal traction at the edges of the hole. (d) Long-term postoperative cross-sectional b scan of the corresponding macula with the MH closed; there is diffuse retinal thinning of the inner layers of the retina. (e) Preoperative perfusion evaluation at the SVP with the perfusion index values in the different subfields of the macula in the key to the left. (f) Comparative postoperative lower perfusion values at SVP. (g) Preoperative FAZ area. (h) Long-term postoperative FAZ area. (i) Preoperative choroidal perfusion indices. (j) Comparative long-term postoperative choroidal perfusion indices.

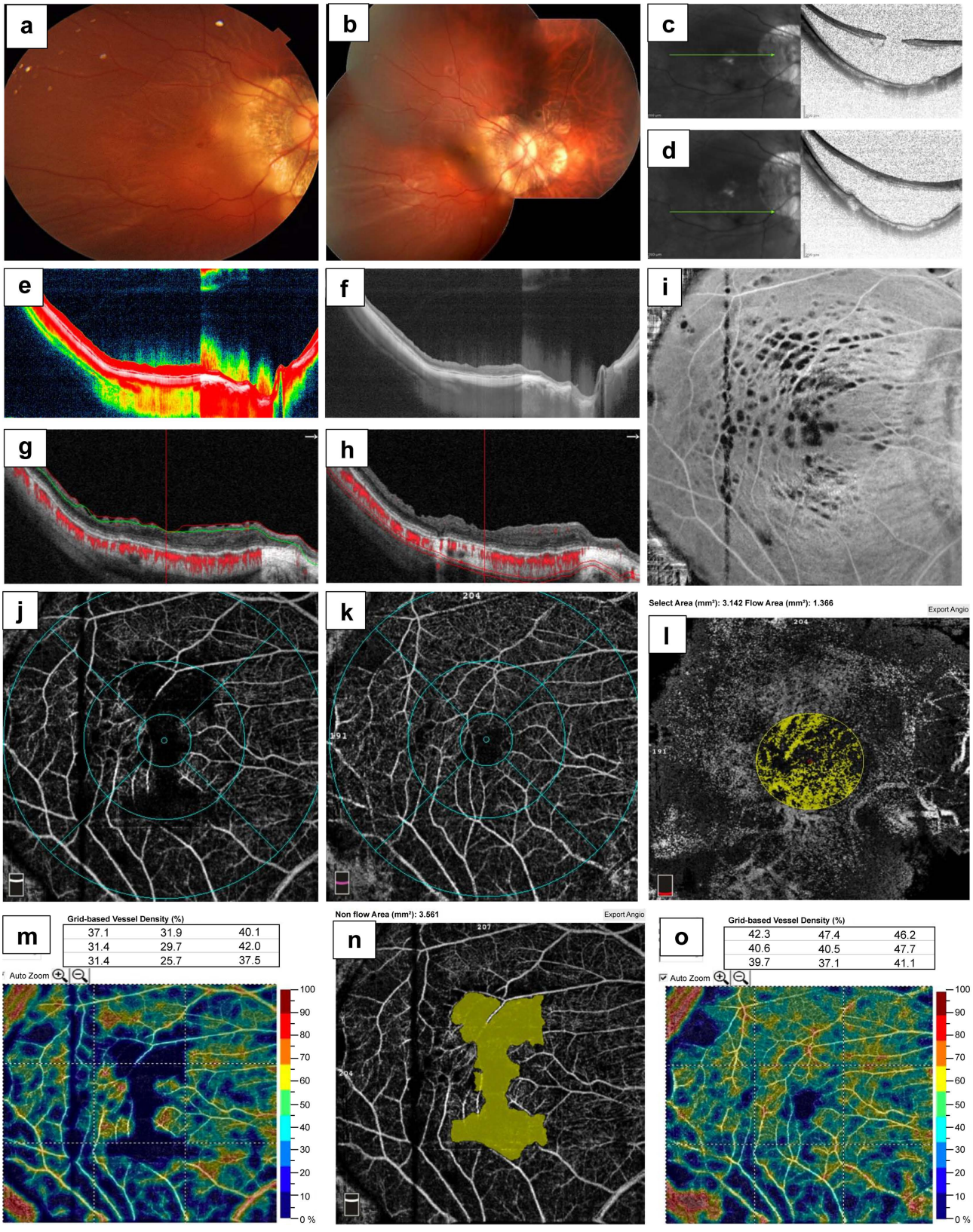

Figure 6. *Surgical case 4*. (a) and (b) Images depicting color fundus photos of a 56-year-old woman with two months of slowly progressive decreased vision with metamorphopsia, high myopia, and an extensive rhegmatogenous retinal detachment in three quadrants associated with a macular hole. (c) and (d) Images of a Spectralis B scan examination consistent with retinal detach-

ment and the confirmed presence of a full-thickness macular hole. This patient underwent 25-G three-port pars plana vitrectomy and macular surgery consisting of the BBG dye-assisted ILM-peeling technique (inverted-flap ILM-peeling technique) after reapplication of the detached retina and a 15% C_3F_8 long-acting nonexpandable gas tamponade. The preoperative BCVA was 20/800 (logMAR 01.60), with PS and an axial length of 31.40 mm. (e) and (f) Fourteen-month postoperative images depicting high-definition 12 mm horizontal scans in brighter color and grayscale with the retina totally reattached and the macular hole closed, abnormal macular profile, presence of SD-OCT biomarkers such as inner and outer retina SD-OCT layers, disrupted subfoveal IS/OS (ellipsoid zone), irregular external limiting membrane line and a well-preserved RPE layer. (g) and (h) Images depicting automated red and green segmentation lines with dissociated optic nerve fiber layer (DONFL) defects and irregular thinning of the inner layer of the retina. The red dots represent choroidal flow. (i) Image depicting the en face aspect of multiple deep defects at the level of the RPE and choroid. After a 14-month follow-up, the final postoperative BCVA was 20/100 (logMAR 0.70). (j) and (k) Images depicting superficial and deep vascular plexuses considered lower than normal at the deferent macular subfield in the ETDRS grid over the OCT angio slabs. (l) Image depicting a deficient choriocapillaris flow index of 1.366 mm^2 considered under the mean value. (m) and (n) Images showing an irregular and enlarged superficial foveal avascular zone of 3.561 mm^2. (o) Image showing the vessel density expressed as the percentage at the 9 different macular quadrants denoted as lower than the mean perfusion indices.

level (and its defined subregions) at different stages of MTM. Thus, we compared perfusional indices obtained from a set of successfully surgically resolved MTM eyes at different stages as well as with the group of emmetropic and myopic eyes from a demographically matched set of control patients. The study combined and examined data from a number of saved ILM and removal techniques; yet we did not observe statistically significant differences in the postoperative quantitative perfusion indices between techniques. The study found a significantly decreased choroidal perfusion in myopic eyes in accordance with an earlier study by Al-Sheikh *et al.* [39]. OCT measurements also revealed choroidal thinning in the macular region of myopic eyes, corroborating its status as a putative aging-related degenerative high myopia. Previous studies suggest that subfoveal choroidal thinning is characteristic of the early stages of MTM and may precede the development of retinoschisis [12] [26] [40].

Many of the patients at the early stage of the MTM disease (*i.e.*, Stage 1) or MF remain fairly asymptomatic with relatively preserved visual acuity for years [32] [41]. Therefore, we agree with recent claims by Takano and Kishi [23], Shimada *et al.* [19] and Ichibe *et al.* [41] who identified MF as the earliest stage or direct precursor lesion of FRD. Uchida *et al.* [22] demonstrated that at this stage, 80% of the cases resolved with only vitrectomy and gas tamponade, and in the remaining cases, ILM peeling techniques were required. The present study found total resolution of foveoschisis in surgically treated eyes; a modified ILM peeling technique was implemented, resulting in good anatomical and functional outcomes. None of the studied eyes showed progression to FRD or partial MH during the follow-up period. Recent studies [42] found gradual progression of MF to FRD in 41% of patients over a 12-month period. Another study estimated the rate of progression from early stage MTM to FRD at 34.5%, with progression to partial-thickness MH observed in 20.7% of the patients [16]. The appearance of focal irregularities and external retinal thinning preceded the formation of an outer lamellar defect associated with focal retinal detachment. The progression of the defect is enhanced by the traction exerted by column-like structures,

leading to the elevation of the upper retinal edge and FRD enlargement [42] [43]; FRD has been reported to occur in around 9% of myopic eyes with PS [44].

Studies indicate that MF resolution can be achieved only surgically via a vitrectomy, posterior vitreous cortical remnant removal and gas tamponade with or without ILM peeling [16] [24] [45] [46] [47] [48] [49]. Panozzo and Mercanti [7] argue that the abolition of vitreoretinal traction during the early stages of the disease would enable the re-flattening of the macular center. Correspondingly, the intervention is expected to prevent development of full-thickness MH, motivated by the elevated prevalence of an ERM in highly myopic eyes with MF/FRD. The current study is contributing to the emerging literature by reporting on the results of quantitative perfusional and qualitative evaluations that utilized fluorescein angiography and quantitative angiographic VD measurement using the AngioVue with OCT as outlined by Wang *et al.* previously [20]. Choroidal perfusion is supported by the intactness of the VD in the capillary layer and helps maintain a stable MF, preventing MTM progression and FRD formation [49]. Reductions in macular VD and resulting decreases in choroidal perfusion in highly myopic eyes are hypothesized to stem from stretching forces driven by the elongation of the eyeball [39]. Epifoveal ILM-sparing techniques compare favorably to those that require ILM peeling and are more likely to prevent MTM progression, likely due to ILM being the basement membrane of foveal Müller cells [27] [50] [51].

The current study capitalized on the accuracy and reliability of quantitative OCT angiography-based perfusion indices of macular microcirculation under the assumption that even mild microcirculatory changes may lead to pathological alterations and impaired vision [52]. Changes in small vessels and decreases in vascular density indices have previously been documented across the spectrum of retinal vascular diseases, including diabetic retinopathy, macular telangiectasia, and radiation retinopathy [53] [54] [55]. Our analysis revealed a positive association between the primary visual acuity outcome BCVA and the CFA. BCVA also tended to negatively correlate with CSFT: analysis done in logMAR units suggested negative correlation with the CFA and a positive correlation with CSFT, although the results did not reach statistical significance. Analyses performed within the surgically treated group examined the associations between the pre-post change in BCVA and various biomarkers, but none was statistically significant. We also found that structural defects in the EZ tended to positively correlate with the superficial FAZ area and ELM line defects, which tended to negatively correlate with the mean deep whole macular VD index. Thus, the study presents new findings linking visual outcomes and normal-range vessel changes in normal emmetropic eyes, healthy highly myopic eyes, and surgically resolved cases across different stages of the MTM spectrum. These results are promising and highlight utmost clinical utility of quantitative perfusional evaluations but require further independent validation given the limited sample size. We did not observe significant changes in macular perfusion indices between the

study and control groups or significant differences in the quantitative perfusion indices evaluation among the different stages in MTM study group. Notably, we found a statistically significant and pronounced effect when comparing the quantitative VD indices of the microcirculation of the macula between the healthy control and the surgically resolved MTM groups ($P < 0.001$). These findings further the empirical evidence linking tractional mechanisms and perfusional mechanisms of MTM development in high myopia but do not resolve the temporal physiopathogenic order.

In this study, perfusional indices obtained from paracentral subfields were not affected by the FAZ; likewise, FAZ had a modest impact on the complete macular area evaluation (as noted by You *et al.* [56]). Thus, quantitative evaluation of macular VD in the paracentral macular area appears to be as reliable as measuring the entire vascular macular area. Peng *et al.* [57] suggested that fovea-sparing ILM removal upregulates local cytokine production and release, altering the vascular microenvironment and permeability and driving the resolution of FRD. Our study provides further insights into the pathophysiology of different stages of MTM and suggests that microcirculation plays an important role in MTM's tractional pathogenesis.

Choroidal perfusion indices have been previously found to correlate with VD values. Correspondingly, transoperative perfusional alterations or compression of the choroid secondary to macular buckling surgery can further interfere with perfusion (*i.e.*, the flow index) in this population of patients with advanced stage MTM temporarily or permanently, respectively [20]. FAZ distortion along with the enlargement of the juxtafoveal capillary net contribute to decreased perifoveal VD in MF. Both our study and a study by Hwang *et al.* [49] established a positive significant correlation between BCVA and mean macular perfusion indices in the SVP and the 1 mm selected foveal area of the choroid capillary layer across the different stages of MTM in the postoperative perfusion evaluation. However, the effect was absent in healthy myopia. In other words, choroidal capillary VD anomalies and low choroidal thickness itself may not directly impact vision. Further research is needed to elucidate the mechanisms behind this observed heterogeneity.

The study results suggest increased need for advanced surgical techniques at later stages of MTM, especially those related to the ILM manipulation or its free flap transplantation. Analyses of quantitative perfusion indices identified more microcirculatory alterations and consequently lower perfusion associated with advanced stages of MTM.

Most of Stage 2 MTM patients with FRD are symptomatic with metamorphopsia and display some progressive vision loss. Recent recommendations suggest that better and modified techniques, such as fovea sparing ILM peeling are applicable in both refractory and primary cases, resulting in foveal reattachment and significant visual improvement [25] [28] [29] [32]. Shimada *et al.* [27] developed the fovea-sparing ILM removal technique; no eyes developed MH af-

ter treatment, compared to 16.7% of eyes developing a full-thickness MH after treatment with the classical technique. Gaucher *et al.* [21] [22] [23] [24] reported FRD in 10 (34.5%) of 29 eyes. The presence of MF and FRD is considered predictive of poor prognosis and MH formation by some authors [16] [23] [25] [45]. We view this as a case of impending MH formation instead [58]. Only a limited number of eyes treated with these techniques progressed to MH formation in the current study, compared with the FRD eyes that underwent classical ILM peeling.

The development of a full-thickness MH may be spontaneous as a part of the natural course of the disease or secondary to the classical ILM removal, as mentioned by some authors [10] [23] [25] [45]. Gaucher *et al.* [24] suggested distinct pathophysiological mechanisms behind these processes. Myopic eyes with total posterior vitreous detachment are subject to the traction exerted by cortical remnants adhering to the macula. Formation of an MH is always preceded by FRD, attributable to the extreme foveal thinning and the tangential traction exerted by a tense ILM, or persistent posterior vitreous remnants. In this study, better vision was ultimately achieved in eyes treated with ILM modified inverted-flap technique regardless of the tamponade used. However, there was no significant difference between the surgical techniques or types of tamponades used in perfusion indices. Thus, the carefully modified inverted-flap ILM manipulation technique seems to be of paramount importance for MH closure and is associated with better functional outcomes.

Retinal detachment in the presence of and associated with MH formation is challenging from the standpoint of treatment approach selection. Several surgical approaches have been described, including gas and silicone oil tamponade, additional laser treatment of the hole margin, and episcleral buckling of the macula area [59] [60] [61]. Vitrectomy with long-acting gas for eyes with MHRD is successful in between 45% and 68% of cases, with rates of up to 79% and 89% described with silicone oil as tamponade [62] [63] [64] [65] [66]. As mentioned by others [64], chorioretinal degeneration and RPE atrophy contribute to issues in reapplication of the retina and poor visual recovery at later stages of the disease, such as in the Stage 4 (MHRD) group in the present study. Severe alterations in macular perfusion and microcirculation likely contribute to poorer outcomes in this group once the macula has been reattached. ILM or its remnants contribute to the delayed closure or reopening of MH and retinal detachment, as suggested by Kadonosono *et al.* [46] who found that myofibroblasts on the ILM surface can contract around MH.

Removing the ERM/ILM complex as the central factor predicting hole closure is hypothesized to improve the flexibility of the detached retina and MH healing even in the presence of PS [67] [68] [69]. Several recent reports have emphasized the importance of appropriate ILM manipulation under intraoperative microscope-integrated SD-OCT to enhanced control in ERM and ILM striping [70] [71].

The study had a number of limitations characteristic of retrospective studies

of limited sample size. We note that this was due to the application of strict exclusion criteria designed to limit our study to successfully surgically corrected eyes in the different stages of MTM. However, it capitalized on a well-controlled and matched group design and the utilization of SD-OCT and OCT angiography, coupled with the examination of the visual outcomes and their association with perfusional indices. We hope that the scientific retina community finds our report useful and timely given the sparsity of published material on perfused macular assessment in this condition.

The strengths of the study also include collection of data on disease occurrence in a significant number of fellow eyes, and early detection of changes. The study found that the fellow eyes showed significantly better postoperative final BCVA values. Importantly, most of these eyes underwent surgery at early stages, leading to better functional and perfusional results. There were no fellow eyes that underwent surgical intervention at stage IV (MHRD); 85.71% of fellow eyes were treated at an early stage of MTM.

In summary, the combination of results related to perfusion, structural and functional evaluations in this study found overall better visual improvement in eyes with MTM that were treated at an early stage, compared to more advanced stages. Likewise, perfusion indices were significantly lower when the eyes were operated on at an advanced stage or when they underwent more than one surgical procedure. Analyses of prevalence of MTM and need for surgery in the second eye found that highly myopic patients are at a high risk of developing a profound and irreversible loss of vision when they undergo surgery in late stages of the disease. This was particularly true when abnormalities in the perfusion indices were detected in the postoperative period and led to poor vision recovery.

5. Conclusion

Surgically-resolved MTM eyes generally exhibit larger superficial postoperative FAZ, smaller CFA, lower VD, more structural macular defects, and thinner CSFT on OCT evaluation when compared to normal emmetropic and healthy myopic eyes. Eyes with stage III or IV MTM had larger deviation compared to eyes at earlier stages. Visual function change after surgery was correlated with superficial foveal avascular zone area. Better functional, and perfusion index outcomes were observed when highly myopic eyes underwent timely surgery. Thus, careful prospective and longitudinal evaluations of highly myopic and fellow eyes are advised to detect early stages of MTM to optimize the decision making related to the choice of the best macular surgical technique in each case. Further prospective randomized clinical trials will be needed to elucidate the pathogenesis of MTM and determine the most appropriate surgical procedures to address and prevent this severe and debilitating condition.

Acknowledgements

We express our deep appreciation to the technical staff of the Retina Specialists

Unit at Oftalmologia Integral ABC (Nonprofit Medical and Surgical Organization) Mexico City, Mexico, which is affiliated with The Postgraduate Division Studies at the National Autonomous University of Mexico.

Author Contributions

MAQR, study conception, writing the manuscript, dataset interpretation, statistical analysis interpretation, conclusions, final revision; EAQG, figures artwork, tables, photographic material compilation; MAQG, graphics, statistical analysis; VLG, statistical analysis, final revision. All authors approved the manuscript for submission.

Funding

No funding or grant support was received for this study.

Institutional Review Board Statement

This study was conducted in the Retina Department at Oftalmologia Integral ABC Institution, Mexico City, Mexico. The institutional review board approved the study per institutional guidelines; no reference number is provided for retrospective studies by this institution.

Data Availability Statement

The datasets from this study are included in the main article. Photos and figures from this study may be released via written application to the Photographic Laboratory and Clinical Archives Department of the Retina Specialists Unit at Oftalmologia Integral ABC, Medical and Surgical Assistance Institution (nonprofit organization), Av. Paseo de las Palmas 735 suite 303, Lomas de Chapultepec, Mexico City 11000, Mexico, and the corresponding author upon request. All of the analysis files and figures (pdf, eps, tiff) can be found at the following Supplementary file all of the analysis files and figures (pdf, eps, tiff) can be found at the following link:
https://www.dropbox.com/sh/dx0ig568houbkwg/AACj-AvLmW9XOC2pL8n7_NQka?dl=0.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Table S1. Correlation analyses with BCVA.

	Coefficient estimate	Std. Error	P value[a]
Superficial FAZ area	0.029432	0.0823	0.721231
Superficial foveal VD	0.01164	0.007505	0.123457
Deep foveal VD	−0.0123	0.008353	0.143257
Superficial parafoveal VD	−0.01839	0.013467	0.174563
Deep parafoveal VD	0.003908	0.014757	0.791562
Superficial whole-macula VD	0.001586	0.01407	0.91045
Deep whole-macula VD	−0.00627	0.015801	0.692299
CFA	−0.14168	0.069464	0.043495

[a]Adjusted P values < 0.05 are highlighted in gray. BCVA: best corrected visual acuity, CFA: choriocapillaris flow area, FAZ: foveal avascular zone, VD: vessel density.

Table S2. Correlation analysis with change in BCVA.

	Coefficient estimate	Std. Error	P value[a]
Superficial FAZ area	−0.23678	0.108903	0.032641
Superficial foveal VD	0.021504	0.014501	0.142019
Deep foveal VD	−0.00727	0.015772	0.646134
Superficial parafoveal VD	−0.00526	0.019355	0.786597
Deep parafoveal VD	0.045014	0.023161	0.055467
Superficial whole-macula VD	−0.03708	0.022449	0.102498
Deep whole-macula VD	−0.01217	0.022497	0.589995
CFA	0.029959	0.119834	0.803228

[a]Adjusted P values < 0.05 are highlighted in gray. BCVA: best corrected visual acuity, CFA: choriocapillaris flow area, FAZ: foveal avascular zone, VD: vessel density.

Table S3. Correlation analysis with CSFT.

	Coefficient estimate	Std. Error	P value[a]
Superficial FAZ area	12.12241	9.745091	0.217106
Superficial foveal VD	3.1662	1.296561	0.016784
Deep foveal VD	−1.82231	1.409868	0.199845
Superficial parafoveal VD	−1.50448	1.732746	0.387816
Deep parafoveal VD	−1.44119	2.072449	0.488792
Superficial whole-macula VD	2.317136	2.001291	0.25034
Deep whole-macula VD	1.369357	2.000286	0.495563
CFA	5.582436	10.71017	0.60363

[a]Adjusted P values < 0.05 are highlighted in gray. CSFT: central subfoveal thickness, CFA: choriocapillaris flow area, FAZ: foveal avascular zone, VD: vessel density.

Table S4. Correlation analysis with ellipsoid zone defects.

	Coefficient estimate	Std. Error	P value[a]
Superficial FAZ area	0.303649	0.156077	0.055183
Superficial foveal VD	0.03115	0.020766	0.137478
Deep foveal VD	−0.03391	0.02258	0.137023
Superficial parafoveal VD	0.015817	0.027752	0.57028
Deep parafoveal VD	−0.02563	0.033192	0.442278
Superficial whole-macula VD	0.082885	0.032053	0.011503
Deep whole-macula VD	−0.083	0.032037	0.011352
CFA	−0.15003	0.171534	0.384352

[a]Adjusted P values < 0.05 are highlighted in gray. CFA: choriocapillaris flow area, FAZ: foveal avascular zone, VD: vessel density.

Table S5. Correlation analysis with external limiting membrane line defects

	Coefficient estimate	Std. Error	P value[a]
Superficial FAZ area	−0.12694	0.135478	0.351542
Superficial foveal VD	0.01827	0.018025	0.31379
Deep foveal VD	0.000158	0.0196	0.993581
Superficial parafoveal VD	0.041901	0.024089	0.085757
Deep parafoveal VD	−0.08165	0.028812	0.005803
Superficial whole-macula VD	−0.0044	0.027822	0.874688
Deep whole-macula VD	0.014054	0.027808	0.614671
CFA	−0.27117	0.148895	0.072267

[a]Adjusted P values < 0.05 are highlighted in gray. CFA: choriocapillaris flow area, FAZ: foveal avascular zone, VD: vessel density.