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Association between Macular Pigment Optical Density and Visual Recovery after Macular Hole Closure

Maria Hernandez[1]*, Carlos Vega[1]

[1]Department of Medical and Clinical Innovation, University of Valencia, Valencia, Spain.

Abstract

The current investigation examined the significance of macular pigment optical density (MPOD) in individuals with full-thickness macular hole (FTMH) compared with healthy volunteers. It also aimed to monitor changes in MPOD following surgery and to determine any potential links between these changes and final visual performance. This prospective, cross-sectional, comparative analysis included 16 eyes of patients with FTMH who achieved complete anatomical closure after pars plana vitrectomy with the inverted ILM flap procedure. All eyes received a thorough eye examination consisting of best-corrected visual acuity (BCVA) testing, intraocular pressure measurement, anterior segment assessment, fundus inspection, and detailed macular imaging via Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT, Spectralis, Heidelberg Engineering Inc., Heidelberg, Germany). Macular pigment optical density (MPOD) was assessed using one-wavelength reflectometry (Visucam 200, Zeiss Meditec, Jena, Germany). Evaluations were performed before surgery and at 1, 3, and 6 months after surgery to assess changes over time and investigate associations between MPOD and visual outcomes. At baseline, clear differences existed between the FTMH and control groups in BCVA, mean MPOD, maximum MPOD, and MPOD volume ($P < 0.05$). After the procedure, BCVA showed a notable improvement ($P = 0.0011$), while MPOD volume increased significantly by the 6-month follow-up ($P = 0.01$). A robust positive relationship was detected between the extent of BCVA improvement and the growth in MPOD volume ($r = 0.739$; $P = 0.002$). Overall, incorporating MPOD measurement into the postoperative care of FTMH cases may provide valuable supplementary information on photoreceptor condition and macular metabolic processes, which may be linked to the degree of visual restoration. More extensive, long-term research is warranted to better understand its connections with various clinical aspects, including metamorphopsia and fine structural details observed on OCT.

Keywords: Macular pigment optical density, Full-thickness macular hole, Visual recovery, Inverted ILM flap

Corresponding author: Maria Hernandez
E-mail: maria.hernandez@gmail.com

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Introduction

A full-thickness macular hole (FTMH) is a serious retinal disease characterized by a complete defect through the foveal center. This leads to major central vision decline accompanied by distorted vision known as metamorphopsia [1]. The condition impacts about 0.09% of the population [2] and occurs most frequently in people in their sixties [3], showing a greater tendency in females [4]. If not addressed, FTMH frequently causes lasting visual deficits [5]. Improvements in surgical approaches, notably pars plana vitrectomy with internal limiting membrane (ILM) peeling or the inverted flap method, have markedly boosted success rates for hole closure and enhanced visual outcomes for many patients [6]. Even so, some individuals continue to experience partial visual gains and ongoing visual distortion, possibly due to minor, lingering structural irregularities after the operation [7].

In recent times, optical coherence tomography (OCT) and fundus autofluorescence (FAF) imaging have proven useful for assessing structural repair. Apart from these structural assessments, attention has increasingly turned toward functional indicators such as macular pigment optical density (MPOD), which can deliver extra details on the wellbeing and metabolic state of photoreceptors in the macular zone.

This study aimed to compare macular pigment optical density (MPOD) levels in patients with full-thickness macular hole (FTMH) with those in healthy control subjects, to record postoperative changes in MPOD, and to analyze how these changes relate to expected visual outcomes. The importance of this method lies in its ability to broaden insight into both the anatomical and functional aspects of healing in FTMH patients, thereby establishing MPOD as a potentially useful prognostic factor that works alongside routine imaging tools.

Materials and Methods

Study design and setting

This prospective, cross-sectional, comparative study was conducted at the Eye Clinic of the University of Naples "Federico II" from July 2023 to April 2024. The protocol received retrospective registration on ClinicalTrials.gov (NCT06664515) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent before joining the study, and full respect for confidentiality and data protection rules was maintained.

Participants

The study enrolled adults aged 18 or older who had been referred to the vitreoretinal clinic for a confirmed full-thickness macular hole (FTMH). These individuals underwent surgical repair using the inverted ILM flap procedure and showed complete closure of the hole postoperatively **(Figure 1)**. Cases were ruled out if there was any record of congenital eye abnormalities, uveitis, past vitreoretinal surgery or retinal blood vessel problems, choroidal neovascularization, high myopia (greater than 6 diopters), earlier focal laser application or photodynamic therapy (PDT), or any form of prior intraocular operation.

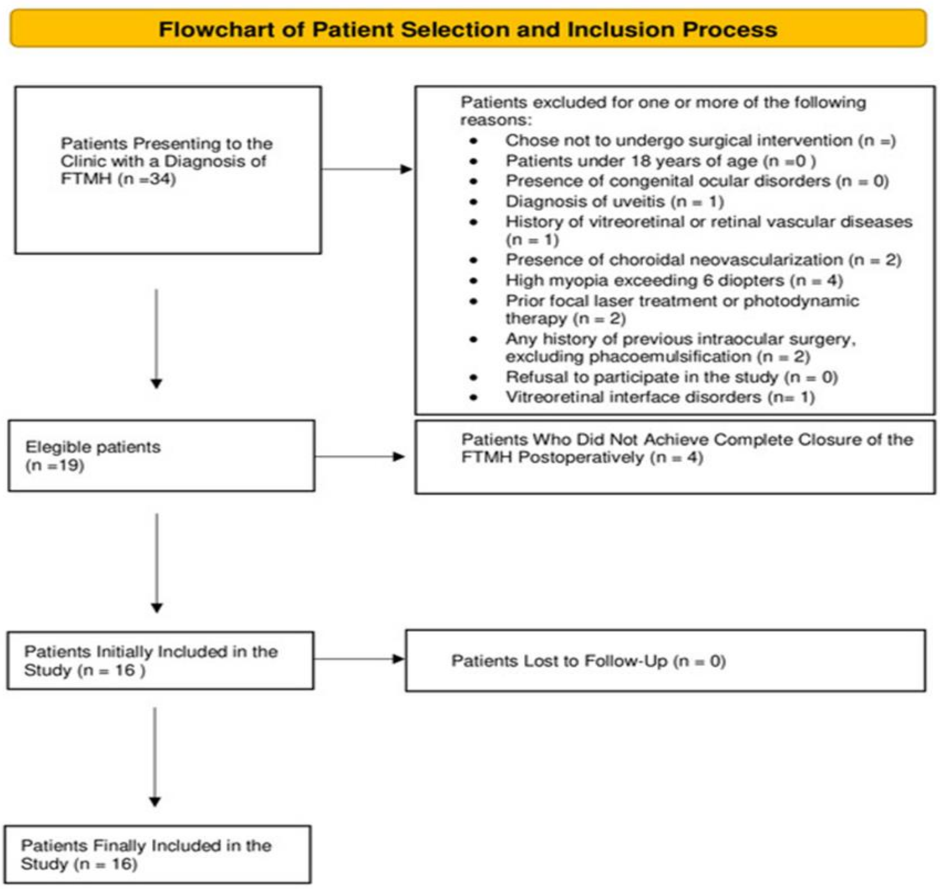


Figure 1. The process of patient selection and inclusion in the study.

Surgical technique

An experienced vitreoretinal surgeon (M.R.) performed all operations using the inverted ILM flap approach. Once the epiretinal membrane had been taken away, forceps were used to seize the ILM and strip it in a round pattern so that it spanned roughly 2 disk diameters centered on the macular hole. After trimming the ILM borders with a vitreoretinal cutter, the remaining flap was turned over to lie across the hole, as outlined by Michalewska *et al*. [6]. The eye was then filled with an air tamponade, and each patient was instructed to remain in a face-down position for 6 days, spending 7 hours daily in that position.

Retinal imaging and data measurement

A thorough eye examination was completed on every participant's eye. This included testing best-corrected visual acuity (BCVA), measuring intraocular pressure, inspecting the anterior segment, viewing the fundus, and scanning the macula using Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT; Spectralis, Heidelberg Engineering Inc.). Macular pigment optical density (MPOD) was additionally quantified by means of one-wavelength reflectometry (Visucam 200, Zeiss Meditec, Jena, Germany). All these evaluations were conducted before the procedure and repeated at 1, 3, and 6 months after surgery to track any shifts systematically over time.

Macular pigment assessment and analysis

Evaluation of MPOD relied on the one-wavelength fundus reflectance technique [8, 9] performed with the Visucam 200 instrument (Zeiss Meditec, Jena, Germany). The system relies on narrow-band blue light reflectance to gauge macular pigment (MP) concentration. Pigment-rich zones take in blue light far more readily than neighboring retinal tissue, so stronger absorption zones show up as darker patches in the resulting blue reflectance pictures, reflecting the elevated optical density of the pigment.

Subjects placed their foreheads on the upper support bar and rested their chins on the designated rest to keep the head steady, while chin-head straps helped maintain the correct position. A central internal fixation point further supported alignment. One drop of 1% tropicamide was administered to widen the pupils, after which 45° color fundus images were obtained 30 minutes later. Blue light illuminated the retina, and the MPOD image was recorded only via the blue channel to limit crossover from green-channel autofluorescence.

Measurement covered a 30° area within the fundus image, using an automatic flash with an intensity setting of 12 and autofocus enabled. Analysis focused on the ring-shaped zone from 4° to 7° eccentricity relative to the fovea, the main location where xanthophyll pigments concentrate. This zone was separated from the outer background area beyond 7° eccentricity, which lacks macular pigment. Dedicated software processed the images to yield optical density readings and pigment layout, extracting four key metrics per picture: (a) mean MPOD together with its reproducibility; (b) the highest MPOD reading; (c) MPOD area, defined as the surface where pigment presence was identified against the background; and (d) MPOD volume, representing the summed optical density throughout that area. Mean MPOD gives the average xanthophyll density across the examined surface, while maximum MPOD captures the peak value, which is most often located at the foveal center. All MPOD results are given in density units (du).

Variables and outcomes

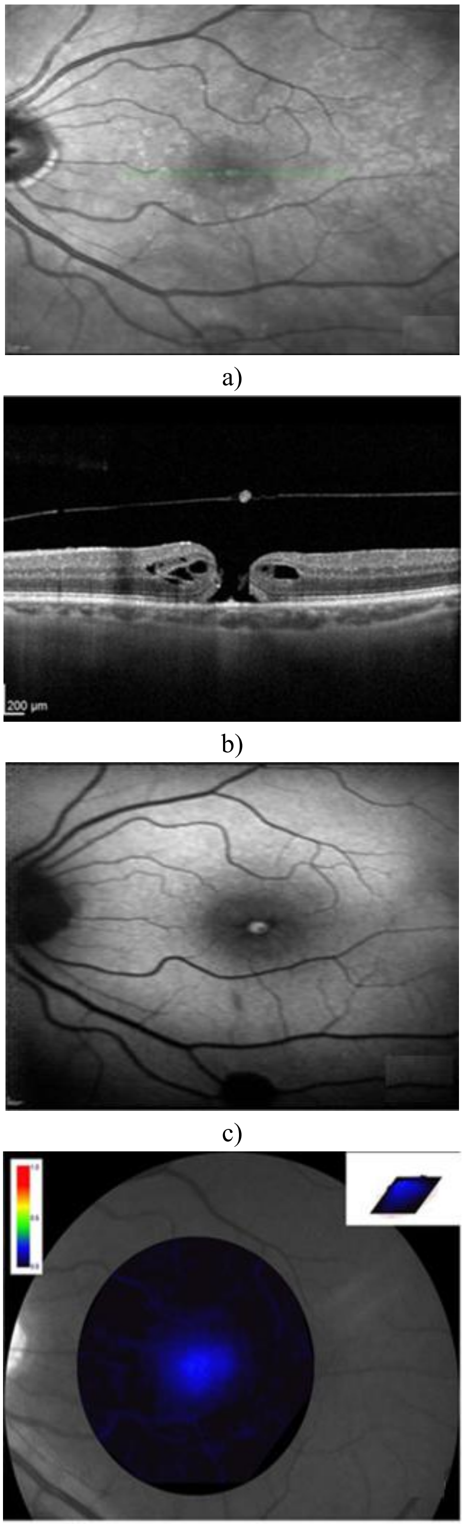
Initial patient information was set against corresponding data from a group of healthy, age-matched control volunteers. These controls came from people attending standard health screenings. They satisfied the very same exclusion standards used for the FTMH group: no congenital ocular disorders, no uveitis, no prior vitreoretinal or retinal vascular conditions, no choroidal neovascularization, no high myopia (greater than 6 diopters), no history of focal laser treatment or PDT, and no record of any earlier intraocular surgery. Next, comparisons examined variations in best-corrected visual acuity (BCVA), mean MPOD, maximum MPOD value, MPOD area, and MPOD volume across the postoperative time points up to the 6-month check. In the end, the links between the MPOD readings and improvements in both structural and visual function were investigated in detail.

Statistical analysis

Data processing was performed using Stata 11 (StataCorp, 2009; Stata Statistical Software: Release 11, College Station, TX, USA). Group differences were tested via an unpaired t-test. To explore connections between mean MPOD and best-corrected visual acuity (BCVA), Pearson correlation coefficients (r) were determined. Linear and nonlinear (second-order) regression analyses, supported by analysis of variance (ANOVA), provided deeper insight into those links. Any result with a p-value below 0.05 qualified as statistically significant.

Results and Discussion

This investigation analyzed data from 16 eyes from 16 individuals who met the entry requirements. Participants averaged 61.5 ± 8.7 years in age. Before any intervention, the group's mean best-corrected visual acuity (BCVA) registered at 1.5 ± 0.5 logMAR units. Every eye showed intraocular pressure (IOP) at or below 18 mmHg. The anterior eye structures appeared healthy, featuring transparent corneas and pupils that responded appropriately to light. Within the cohort, seven cases (43.8%) were already pseudophakic following prior lens replacement, leaving nine (56.2%) still phakic with their own natural lens intact. Clinical fundus evaluation, supported by various imaging approaches, consistently revealed a substantial full-thickness macular hole (FTMH) in each participant. These holes were documented via en face OCT **(Figure 2a)**, spectral-domain OCT **(Figure 2b)**, and autofluorescence (AF) **(Figure 2c)**.



d)

Figure 2. (a) En face OCT image demonstrates FTMH in the foveal area; (b) OCT imaging of the macula reveals FTMH with marked disruption of all retinal layers, without vitreomacular traction; (c) autofluorescence imaging reveals iperautofluorescence in the macular region; (d) MPOD appears significantly reduced.

On average, the FTMH diameter measured 985 µm ± 150 µm. Initial macular pigment optical density (MPOD) quantification produced these readings: a mean MPOD value of 0.1 ± 0.02 d.u., a peak MPOD of 0.4 ± 0.08 d.u., an MPOD area totaling 63,597.1 ± 16,739.2 pixels, and an MPOD volume of 10,812.6 ± 3329.7 d.u. × pixels.

Surgical repair employing the inverted ILM flap procedure was conducted on all eyes. Phakic cases also underwent concurrent phacoemulsification and intraocular lens (IOL) insertion. Following these steps, every macular hole achieved complete anatomical sealing without exception.

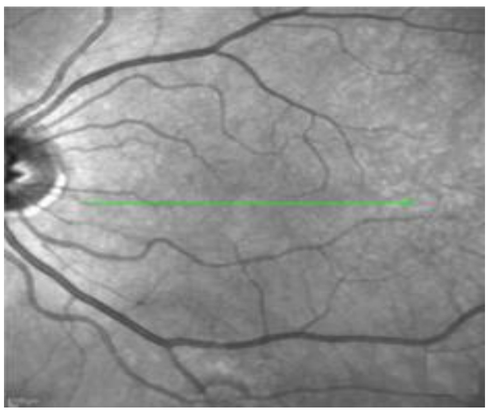
Preoperative comparisons against a group of age-matched healthy volunteers highlighted notable distinctions across several key measures: best-corrected visual acuity (BCVA) (P < 0.001), mean MPOD (P < 0.001), maximum MPOD (P = 0.002), and MPOD volume (P = 0.0006) **(Table 1)**.

Table 1. Characteristics of the study population.

Parameter	Control group (16 Eyes)	FTMH group (16 Eyes)	P-value
Age (years)	62.6 (7.4)	61.5 (8.7)	0.97
BCVA (logMAR)	0.05 (0.1)	1.4 (0.5)	< 0.001
Mean MPOD (d.u.)	0.15 (0.02)	0.1 (0.02)	< 0.0001
Maximum MPOD (d.u.)	0.47 (0.06)	0.4 (0.08)	0.002
MPOD Area (pixels)	80,628.8 (8282.6)	63,597.1 (16,739.2)	0.03
MPOD Volume (d.u. × pixel)	16,338.3 (2822)	10,812.6 (3329.7)	< 0.001

FTMH = full-thickness macular hole; BCVA = best-corrected visual acuity; MPOD = macular pigment optical density; d.u. = density units. Numbers in brackets are standard deviations. P-values in bold indicate statistical significance.

At the six-month postoperative assessment, the macular hole remained fully sealed in all 16 patients **(Figure 3)**.



a)

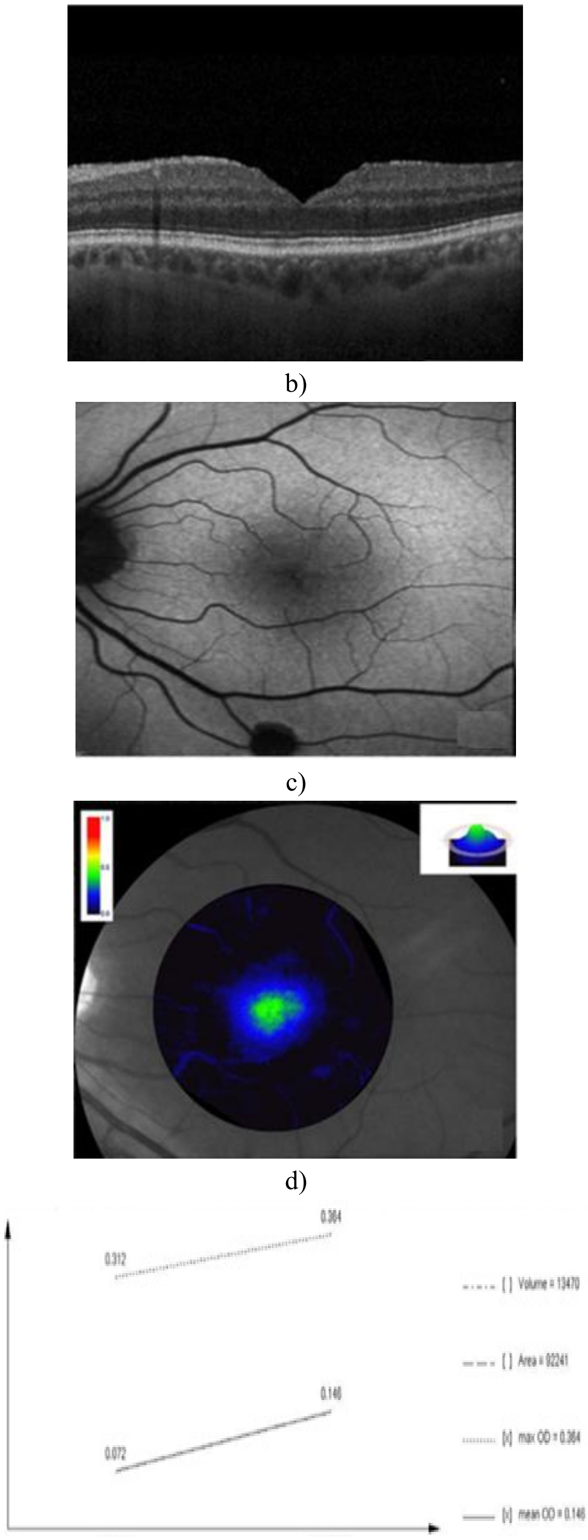


Figure 3. (a) En face OCT reveals a well-closed macular hole (the green arrow indicates the location and orientation of the cross-sectional scan shown in panel b); (b) OCT imaging demonstrates a regular retinal contour, and recovery of central foveal depression, with the successful closure of the macular hole; (c) autofluorescence imaging reveals hypoautofluorescence in the macular region; (d) post-operative MPOD measurements show improved values; (e) the line graph illustrates the temporal variations in the metrics of interest for MPOD, including maximum optical density (max OD), mean optical density (mean OD), MPOD area, and MPOD volume. The arrow in (a) indicates where the OCT scan in (b) is conducted.

Functional vision exhibited substantial gains, advancing from the initial mean of 1.5 ± 0.5 logMAR to 0.7 ± 0.4 logMAR by the final check-up ($P = 0.0011$). Most MPOD-related indices failed to show meaningful statistical shifts after the operation; however, MPOD volume rose markedly, from the baseline of 10,812.6 ± 3329.7 d.u. × pixels to 14,569.1 ± 4764.6 d.u. × pixels ($P = 0.01$). A full overview of all postoperative macular pigment measurements is presented in **Table 2**.

Table 2. Macular pigment optical density changes after surgery.

Parameter	Preoperative value	Postoperative value	P-value
BCVA (logMAR)	1.5 (0.5)	0.7 (0.4)	0.0011
Mean MPOD (d.u.)	0.1 (0.02)	0.1 (0.01)	> 0.9
Maximum MPOD (d.u.)	0.4 (0.08)	0.4 (0.03)	> 0.9
MPOD area (pixels)	63,597.1 (16,739.2)	79,982.5 (25,703.0)	0.2
MPOD volume (d.u. × pixel)	10,812.6 (3329.7)	14,569.1 (4764.6)	0.01

Abbreviations: FTMH = full-thickness macular hole; BCVA = best-corrected visual acuity; MPOD = macular pigment optical density; d.u. = density units. Numbers in brackets are standard deviations. P-values in bold indicate statistical significance.

Additional statistical analysis identified a robust positive association between the extent of BCVA recovery and the observed increase in MPOD volume ($r = 0.739$; $P = 0.002$). Such an association suggests that restored macular pigment levels could support improved visual performance once the FTMH has been successfully addressed by surgery.

Macular pigments (MP), consisting mainly of lutein and zeaxanthin, function as important antioxidants concentrated in the central retina. They contribute significantly by absorbing blue light and scavenging free radicals, which help protect delicate retinal structures against oxidative injury that could otherwise promote the development of various retinal disorders [8, 10]. These carotenoids are effective at neutralizing reactive oxygen species (ROS) generated during oxidative stress. Such ROS can harm the photoreceptor outer segments and the retinal pigment epithelium. By reducing this type of damage, the pigments help maintain both the architecture and the functional capacity of retinal tissue. In addition, lutein and zeaxanthin block high-energy blue light, limiting its ability to trigger photochemical harm in the retina and thereby helping sustain visual sharpness and overall retinal condition. Beyond these actions, the same carotenoids may also limit lipofuscin accumulation while improving lysosomal stability and health [11].

From an anatomical standpoint, macular pigment is found mostly in the Henle fiber layer and the outer plexiform layer (OPL) within the foveal zone, an area packed with cone axons. Further deposits occur in the inner plexiform layer (IPL) of the foveola, within a distinct inverted-cone-shaped arrangement of Müller cells known as the "Müller cell cone," described by Gass [8, 12-14]. Acquired from dietary sources, lutein and zeaxanthin are thought to help delay or prevent the onset of age-related macular degeneration, opening the door to possible dietary approaches to reduce risk [8].

Obana and colleagues suggested that macular pigment consists of two distinct components: one located in the foveolar Müller cell cone and another situated in the Henle fiber layer at the fovea. Individual distribution patterns differ and can appear as a central peak, a ring-like shape, a plateau, or a central dip [14]. In particular, the presence of a central dip pattern, together with reduced pigment density at the foveal center, could signal underlying Müller cell injury and serve as an early warning sign of macular hole formation [14].

Findings after surgery highlight the usefulness of macular pigment as an indicator of healing progress. Procedures to repair full-thickness macular holes (FTMH) that successfully restore normal foveal anatomy frequently result in renewed accumulation of macular pigment and improvements in vision [15, 16].

Multiple investigations have shown that improvements in vision are closely linked to the restoration of normal retinal layers, especially the reconnection of the inner segment/outer segment (IS/OS) junction, which is visible on OCT scans. This anatomical feature consistently predicts stronger visual results [17, 18]. Similarly, fundus autofluorescence (FAF) imaging has revealed that reduced autofluorescent signals in successfully closed macular holes correlate with more favorable visual forecasts [19].

Taken together, these observations suggest that macular pigment optical density (MPOD) can serve as a useful additional indicator, used alongside OCT and FAF, to provide additional information about photoreceptor function and the metabolic state of the macula throughout the recovery phase. Unlike OCT, which primarily captures structural details, MPOD provides a unique functional perspective on how photoreceptors and macular tissue regain health.

A range of techniques is available for assessing macular pigment, including Raman spectroscopy, heterochromatic flicker photometry, fundus autofluorescence imaging, and fundus reflectometry. Among these, fundus autofluorescence evaluates pigment levels according to how macular pigment weakens the fluorescent signal produced by lipofuscin within the retinal pigment epithelium (RPE) [20].

In 2016, Bottoni and co-workers employed Raman spectroscopy in a group of 18 patients who had received macular hole surgery. They reported lower macular pigment levels relative to age-matched healthy eyes, followed by gradual re-accumulation once the hole had closed successfully [21].

Romano *et al*. highlighted the practical advantages and consistent repeatability of measuring macular pigment using the one-wavelength reflectance approach on the Visucam 200 Zeiss fundus camera. Their work documented a clear drop in macular pigment among eyes affected by vitreoretinal interface problems, including FTMHs [20]. The researchers linked this pigment reduction directly to the disease process, especially the foveal opening and the outward shifting of pigment that follows. They also observed a statistically significant increase in MPOD volume after surgery in FTMH cases. The authors proposed that sealing the hole surface allows cone photoreceptors and their axons to move back toward the center, thereby permitting macular pigment to rebuild in the foveal area [20]. The return and subsequent increase of macular pigment after the operation are viewed as favorable markers of natural healing, reflecting not just structural closure but also the recovery of photoreceptor activity and macular wholeness—elements likely tied to better postoperative visual acuity.

Jordan and colleagues added further confirmation by showing that individuals with idiopathic macular holes experienced notable rises in both maximum MP optical density and MP volume after undergoing pars plana vitrectomy combined with dye-assisted internal limiting membrane peeling. These gains were particularly evident among those with stage 4 FTMH [22].

Although modern surgical approaches, including pars plana vitrectomy with internal limiting membrane peeling and the inverted flap method, have raised success rates for closing FTMH, a subset of patients still achieve only modest visual gains and continue to report persistent metamorphopsia. These ongoing issues are often traced to minor structural irregularities that persist even after successful hole closure [7].

However, the link between the post-surgery rise in macular pigment and improvements in visual acuity remains an active field of investigation. The noted association between better vision and postoperative growth in MPOD volume — particularly when combined with restored IS/OS line continuity — reinforces the idea that MPOD can serve as a useful and supportive predictor of visual outcomes in individuals with full-thickness macular holes (FTMH) [23, 24].

Drawing on these observations, we previously described a single FTMH case that achieved successful surgical closure, in which MPOD levels rose noticeably afterward. That instance suggested MPOD's potential usefulness as an additional biomarker associated with positive visual recovery following such procedures. As a result, we broadened the investigation to include a larger patient group to gather stronger supporting data for this relationship [16]. The current results are in line with that perspective, revealing that increases in MPOD volume reliably correspond to gains in best-corrected visual acuity (BCVA) among a uniform cohort of stage 4 FTMH patients treated with 25G pars plana vitrectomy and internal limiting membrane peeling. This indicates that MPOD, thanks to its straightforward and repeatable nature, may be a worthwhile parameter to incorporate into routine monitoring after macular hole repair, providing prognostic information on vision that complements conventional assessment tools.

The present analysis was limited to Caucasian participants. Of note, multiple reports indicate that ethnic background influences both MPOD values and the pattern of macular pigment distribution [25], with studies documenting racial variations — specifically, Caucasians tending to display markedly lower MPOD than African Americans and South Asians [26]. In addition, newer research suggests that the body's capacity to incorporate lutein, as reflected in blood and tissue levels, is partly shaped by genetics and largely depends on single-nucleotide polymorphisms (SNPs) across 15 genes involved in lutein and chylomicron processing [27]. Although preoperative MPOD levels may differ because of geographic, ethnic, or inherited factors, our emphasis on tracking changes in pigment density within each subject helps ensure that baseline differences between individuals do not interfere with the interpretation of the findings. Still, additional research involving diverse ethnic groups would be beneficial for examining these variations more thoroughly and assessing their possible clinical relevance.

Conclusion

In conclusion, measuring MPOD shows encouraging promise as a helpful supplement to standard follow-up care for patients who have undergone FTMH surgery, providing additional information about the visual recovery process. This approach delivers a well-rounded evaluation that goes beyond simply checking structural repair and instead sheds light on the return of photoreceptor activity and the restoration of normal macular condition. Given that the technique is easy to perform, highly repeatable, and well integrated with existing imaging methods, more extended longitudinal investigations will be important to examine in greater depth how shifts in MPOD relate to specific clinical features, including the severity of metamorphopsia and detailed microstructural observations on OCT. Establishing such links would create fresh opportunities to refine both diagnostic and predictive strategies for macular holes and other conditions affecting the macula.

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Ethics statement: This study was performed in accordance with the tenets of the Declaration of Helsinki. It was approved by the Ethics Committee of the University of Naples Federico II (No. EC-20/2024) in June 2024.

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