Predicting macular hole closure after ILM peeling using optical coherence tomography

**Disclosure:** *The authors disclose no financial or ethical conflicts with the present study.*

ABSTRACT

**Purpose**: To study the role of preoperative spectral-domain optic coherence tomography (OCT) as a predictor of macular hole (MH) closure after pars-plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling.

**Methods**: Preoperative OCT scans from patients with symptomatic MH were analyzed. MH height, minimum linear dimension and base-diameter were measured, and the macular hole index (MHI: base-diameter/height) and the newly proposed double diameter index (D+D: minimum linear dimension+base-diameter) were calculated. The leverage of these parameters on postoperative MH closure was calculated by multivariate nominal logistic model. Additionally, preoperative best-corrected visual acuity, duration of symptoms, age, and gender were also considered as potential effects in the analysis.

**Results**: A total of 65 patients completed 48-week follow-up. Mean (± SE) preoperative BCVA (logMAR) was 0.91 ± 0.04 and improved significantly to 0.59 ± 0.05 (P<0.001) after 48 weeks. MH closure was observed on 49 out of 65 cases (75%). Mean preoperative MHI was 0.46 ± 0.02; (height = 444.5 ± 7.7 µm; base-diameter = 1057.6 ± 41.1 µm; and size = 475.0 ± 25.1 µm). There was a significant influence of MH base-diameter, D+D and MHI on MH closure (P = 0.0005). We estimated that a high probability of macular closure could be expected for OCTs showing base diameter smaller than 884.2 µm ± 39.0 µm, and this likelihood decreases from this point at ratio of 11.16 % ± 0.84 % / 100 µm.

**Conclusion:** It is possible to estimate the probability of macular closure using pre-operative measurements on OCT images. These estimates could be used to improve patient and surgeon awareness of anatomical success likelihood following traditional ILM peeling. Data from larger cohorts should be used to confirm these results.

**Key-words:** vitrectomy; macular hole closure, SD-OCT, macular surgery, macular hole.

INTRODUCTION

Macular hole (MH) is a pathological condition caused by a host of different forces acting on the vitreoretinal interface and leading to a splitting or dehiscence of the fovea,1 with prevalence varying from 0.1 to 0.4%, depending on the studied population, and is more prevalent in older women,2-5 with a reported incidence of 4 to 9 eyes per 100,000 individuals per year.6,7

The surgical treatment, first described in 1991,8 aims to act upon those pathological forces, allowing for the anatomical closure of the hole,9 and recently, with the improvement of surgical microscope quality and the advent of small-incision vitrectomy systems, along with high-resolution optical coherence tomography (OCT),10 this procedure has become common practice with favorable post-operative outcomes. Vitrectomy with internal limiting membrane (ILM) peeling has become the technique of choice for treating MH,11,12 and has been shown to have a high rate of success, especially in stage 2 and 3 macular holes.12,13

Post-operative hole closure is associated with better probability of visual acuity gain14, and smaller holes have greater odds of anatomical closure following surgery. In this context, pre-operative MH dimensions can be associated with post-operative outcomes.10,15,16

Larger holes remain a surgical challenge, with smaller rates of surgical success,10 and so a number of different techniques that use the peeled ILM, such as the inverted ILM flap17, or other tissues to assist in hole closure have been proposed as surgical approaches in these cases. 17-20 It is still unclear which cases benefit the most from the use of traditional surgery or a modified approach.

The present study seeks to evaluate preoperative OCT image parameters as prognostic factors for the closure of FTMH following traditional vitrectomy with ILM peeling, possibly aiding in the choice of surgical technique to be employed.

METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board, and all participants gave written informed consent before entering into the study.

This study consists of a *post hoc* analysis of patients enrolled in a prospective clinical trial for the surgical treatment of macular holes, that compared best-corrected visual change between concomitant or delayed phacoemulsification in patients undergoing vitrectomy for MH.

All patient consultations, surgeries and data collection were performed in a single instituion. The study enrolled patients with MH and no cataract or with lens opacity lower than grade II cortical or grade II nuclear, according to the Lens Opacity Classification System (LOCS) III, who were scheduled to undergo surgery for MH between January 1, 2015 and November 30, 2016. In the present analysis, we evaluate the preoperative factors that might predict a successful anatomical closure of the macular hole following surgery, specially OCT image measurements.

At baseline, all patients were submitted to a comprehensive ophthalmologic consultation and spectral-domain OCT imaging (Spectralis Eyetracker Tomographer, HRA-OCT, Heidelberg, Germany).

The MH’s center was detected using the line scanning ophthalmoscope image, and SD-OCT horizontal cross-sectional images were obtained through it. Retinal cross-sectional images were acquired using a standard 20° x 15° raster scan protocol of 19 horizontal scans with a distance of 240μm between each of them, initially centered on the fovea. Follow-up scans were used during the subsequent visits to guarantee reliable comparisons. Using this on-center OCT image, measurements were taken for the hole’s height (H), minimum linear dimension (MLD) and external base diameter (BD). Height was defined as the distance between the internal limiting membrane at its highest point and retinal pigment epithelial (RPE) layer orthogonally beneath it. Minimum linear dimension (MLD) was defined as the smaller distance between the two edges of retina in the internal region of macular hole. External base diameter (BD) was defined as the length of the RPE layer that was not in contact with the photoreceptors, which is sometimes referred to as the base diameter of the macular hole. Macular hole index (MHI) was defined as height divided by external base diameter (H/BD). Tractional Hole Index (THI) was defined as height divided by minimum linear dimension (H/MLD). A new proposed index, the Double Diameter (D+D) was defined as the sum of the MLD and the BD.

All patients underwent routine 23G vitrectomy using the Constellation System (Alcon, USA) with Brilliant Blue assisted ILM peeling, followed by 15% C3F8 tamponade and 1-week face-down positioning. Patients either received combined phacoemulsification and PPV or PPV and then phacoemulsification at any time during follow-up if significant cataract developed. Significant cataract was defined as opacities of subcapsular ≥1, nuclear ≥3 or cortical ≥3 (LOCS III), if it prevented ophthalmic/OCT evaluation or caused any decrease in visual acuity attributable to the cataract.

Patients were scheduled for follow-up examinations at one, three, six months, nine months and twelve months postoperatively. At these visits, patients underwent complete ophthalmic and OCT examination using the same procedures as used at baseline. Macular holes were considered successfully closed if there was no neurosensory retinal defect at the fovea, with complete rim reattachment on OCT.

Nominal Logistic Regression was applied to investigate influence of the following effects on macular hole closure probability: OCT measurements (base diameter, height and minimum diameter), along with baseline best-corrected visual acuity, diabetes, time since diagnostic and age. This is a multi-level logistic response function using maximum likelihood, therefore, all but one response level is modeled by a logistic curve that represents the probability of the response level given the value of the effects. The probability of the final response level is 1 minus the sum of the other fitted probabilities. Parameters are then compared using the Wald Chi-square test.

Subsequently, a part-defined model (equation 1) was used to estimate the minimal effect with 100% likelihood of macular closure and the slope of probability decrease.

In witch is the probability of macular hole closure as function of : effect; is the maximum effect limit for expected 100% probability of macular hole closure; and is the slope of likelihood decrease.

Statistical significance was set at a value of p<0.05. All analyses were performed using the JMP ® 10 software (SAS Institute Inc. Cary, NC, USA).

RESULTS

A total of 65 eyes of 65 patients that completed the one-year follow-up period were included in this post-hoc analysis. The average age was 65.7 ± 6.0 years old, with 51 females (78.5%) and 14 males (21.5%) included; 60% of the patients were hypertensive and 17% diabetic. The MH was classified as stage 1 in 6.1 %, stage 2 in 24.6%, stage 3 in 38.4% and stage 4 in 30.7% of the eyes. Patients reported visual symptoms, such as decreased visual acuity or metamorphopsia, lasting on average 12.0 ± 11.7 months prior to surgery. Surgical MH closure was achieved in 75.4% of eyes following vitrectomy with ILM peeling. **(Table 1)**

|  |  |
| --- | --- |
|  |  |
| Gender (male: female[female %]) | 14:51 [78.5%] |
| Age (mean SD) | 65.7 ± 6.9 |
| Hypertension (%) | 60 |
| Diabetes (%) | 17 |
| Symptoms(months) | 12.0 ± 11.7 |
| BCVA (logMAR) | 0.96 |
| External Base (µm) | 1057 |
| MLD (µm) | 475 |
| Height (µm) | 444 |
| MH Stage (%) |  |
| 1 | 6 |
| 2 | 25 |
| 3 | 38 |
| 4 | 31 |
| Rate of Closure | 75.4% |

**Table 1: Baseline demographics and characteristics of the enrolled patients, with pre-operative measurements and rate of closure following vitrectomy.**

Thirty- three patients underwent combined PPV and phacoemulsification and thirty-two patients underwent PPV and deferred phacoemulsification. No significant difference between groups was found for demographic, macular hole staging or baseline data. There was no significant difference between groups’ OCT measurements at baseline. Macular hole closure rates were 72% and 75%, for the combined and deferred phacoemulsification groups, respectively, with no significant difference between them (p=0.834, chi-square test). (**Table 2**).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Combined Phaco | Deferred Phaco | p-value |
| Gender (female %) | 79 | 78 | 0.94 |
| Age (mean SD) | 66.8 1.0 | 64.6 | 0.13 |
| Hypertension (%) | 60 | 59 | 0.91 |
| Diabetes (%) | 21 | 12 | 0.34 |
| Symptoms(months) | 11.8 | 12.2 | 0.87 |
| External Base (µm) | 1046.0 ± 61.3 | 980.9 ± 62.2 | 0.45 |
| MLD (µm) | 469.2 ± 34.6 | 473.1 ± 35.1 | 0.97 |
| Height (µm) | 428.5 ± 11.8 | 444.75 ± 11.96 | 0.34 |
| MH Stage (%) |  |  | 0.96 |
| 1 | 6 | 6 |  |
| 2 | 27 | 22 |  |
| 3 | 37 | 41 |  |
| 4 | 30 | 31 |  |
| Rate of Closure | 73 | 75 | 0.83 |

**Table 2: Baseline demographics and characteristics of the enrolled patients that underwent combined or deferred phacoemulsification, with pre-operative measurements and rate of closure following vitrectomy.**

Age, duration of symptoms and combined/delayed phacoemulsification were found to be non-significant for the prediction of MH closure following surgery on both the univariate and multivariate analyses **(Table 3)**

Including all baseline OCT measurements as effects (base diameter; minimal diameter and height) along with the demographic parameters (gender, diabetes and duration of symptoms) to the logistic model, only base diameter significantly influenced MH closure **(Table 3).**

| **Term** | **Parameter** | **ChiSquare** | **P** |
| --- | --- | --- | --- |
| Base-diameter | -0.0056 ± -0.0056 | 6.36 | 0.0117\* |
| Height | 0.0121 ± 0.0121 | 2.31 | 0.1284 |
| Duration of symptoms | -0.0253 ± -0.0253 | 0.61 | 0.4346 |
| Gender | 0.2584 ± 0.2584 | 0.33 | 0.5630 |
| Minimal-diameter | -0.0004 ± -0.0004 | 0.02 | 0.8926 |
| Baseline visual acuity | 0.2033 ± 0.2033 | 0.02 | 0.8954 |
| Diabetes Mellitus | -0.0712 ± -0.0712 | 0.02 | 0.9020 |
|  |  |  |  |

**Table 3: Nominal logistic results using base-diameter, minimum-diameter, height, duration of symptoms, gender, baseline best-corrected visual acuity and diabetes as effects on hole closure.**

***Parameter: Parameter estimated given by the logistic model ± Std Error. Chi-Square: Wald tests for the hypotheses that each of the parameters is zero. The Wald Chi-square is computed as (Estimate/Std Error)2. P: Observed significance probabilities for the Chi-square tests.***

Subsequently, demographic data and baseline visual acuity were removed from the model, and a second logistic regression was performed including only OCT measurements **(Table 4)**. Again, only base-diameter showed statistically significant influence on post-operative macular hole closure.

| **Term** | **Parameter** | **ChiSquare** | **P** |
| --- | --- | --- | --- |
| Base-diameter | -0.0055 ± -0.0055 | 6.60 | 0.0102\* |
| Height | 0.0121 ± 0.0121 | 2.58 | 0.1081 |
| Minimal-diameter | -0.0005 ± -0.0005 | 0.04 | 0.8480 |

**Table 4: Nominal logistic results using only base-diameter, minimum-diameter and height as effects on hole closure.**

The macular hole index (MHI, calculated as height/base-diameter); and a new proposed index called D+D, which is defined as the sum of the external base and the minimum linear dimension, were investigated for their influence on macular hole closure. A significant influence was observed for both MHI and D+D. The choice was made to evaluate and present the MHI as its inverted ratio for **(Table 5).**

| **Term** | **Parameter** | **ChiSquare** | **P** |
| --- | --- | --- | --- |
| Inverted MHI | -2.72 ± -0.79 | 12.00 | 0.0005\* |
| D+D | 0.0121 ± 0.0121 | 10.54 | 0.0012\* |

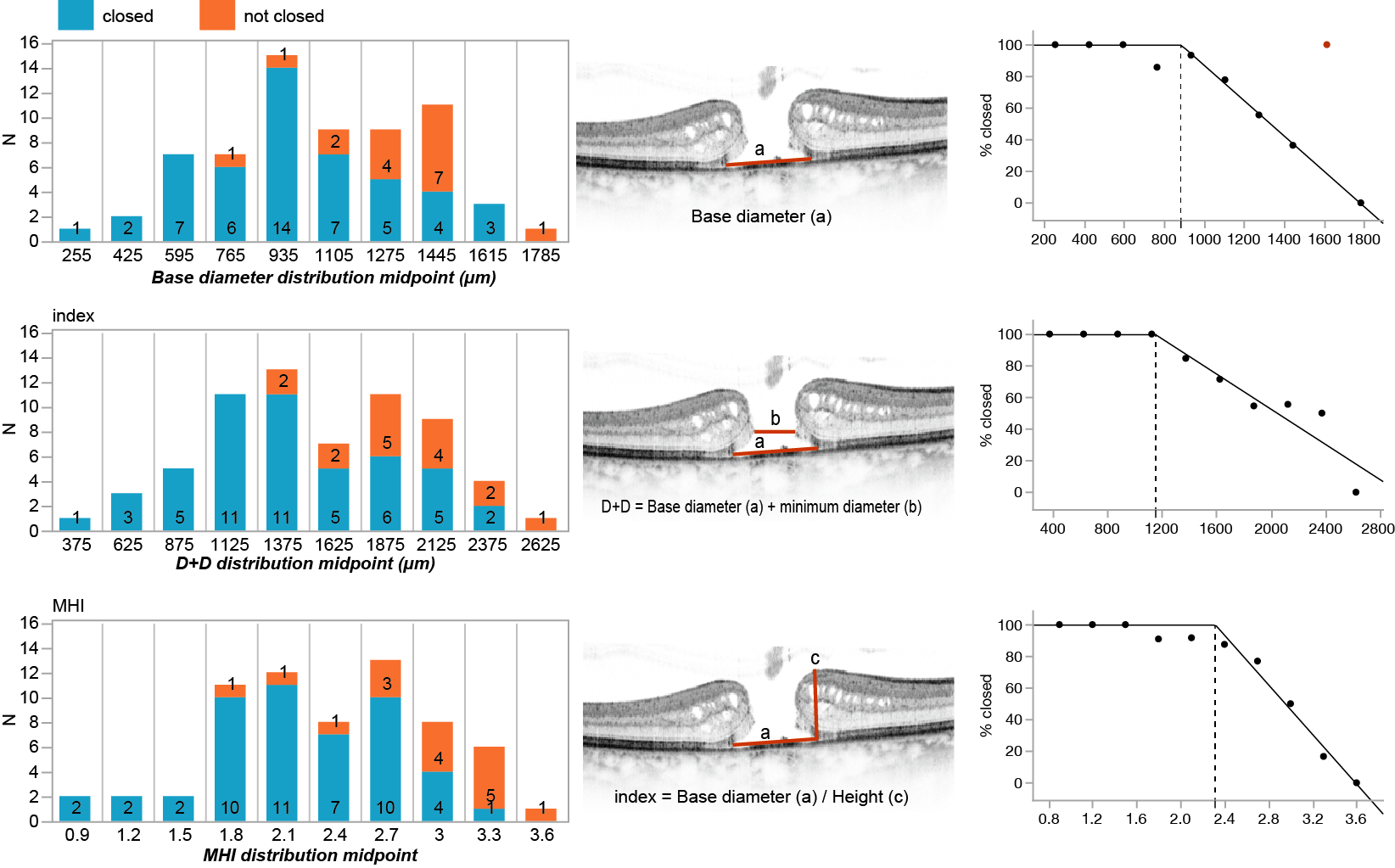
**Table 5: Nominal logistic results using inverted MHI and D+D as effects on hole closure.**

The distribution of closed and unclosed macular holes for the midpoints of BD, D+D and the inverted MHI are shown on the left column of Figure 1. Distribution midpoints were achieved by dividing the data range in 10 blocks. The probability of closure was calculated as the ratio between the number of eyes with MH closure divided by number of eyes for each distribution midpoint.

Next, a part-defined model (Equation 1) was applied to estimate 2 parameters for each of the variables: σ – the maximum limit for an expected 100% probability of macular hole closure; and – the decreasing rate of the likelihood of closure. Parameters were well determined with model convergence for the 3 effects: base-diameter; inverted MHI and D+D (**Table 6 and Figure 1 – right column).**

As a summary, the analysis revealed that high probability of macular closure could be expected for OCTs showing External base diameter smaller than 884.2 µm ± 39.0 µm, and this likelihood decreases from this point at ratio of 11.16 % ± 0.84 % for every 100 µm increase in BD.

For D+D, the high probability of closure is held up to 1148.9 ± 162.4 µm and this likelihood decreases from this point on at ratio of 11.16 ± 0.84 % for every 100 µm increase in D+D.

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**Figure 1: i) the left column shows the distributions of Base diameter, D+D and the inverted MHI, with blue bars indicating closed MH and orange bars unclosed MH for each of the parameter’s midpoints. ii) the center column illustrates how the variables were measured on OCT images. iii) the right column depicts a part-defined model fit to the distribution midpoint averages for base diameter, D+D and inverted MHI.**

| **Label** | **σ (µm)** | **α (% / 100 µm)** |
| --- | --- | --- |
| Base diameter | 884.2 ± 39 [775.4 - 990.5] | 11.2 ± 0.8 [9.2 - 13.6] |
| D+D | 1148.9 ± 162.4 [762.4 - 1486.7] | 5.6 ± 0.9 [3.8 - 8.1] |
| Inverted MHI | 2.3 ± 0.1 [2.1 - 2.5] | 78.4 ± 6.3 [63.8 - 104.3] |

**Table 6: Nominal logistic results using inverted MHI and D+D as effects on hole closure.**

DISCUSSION

The macular hole’s morphology has long been thought to be associated with closure success and visual outcomes following surgical repair; the hypothesis being that bigger defects with chronic changes might have smaller chances of closure and visual gains. The use of OCT as a tool for preoperative evaluation of the lesions began as an extension of the original classification of the disease by Gass 9 and has evolved over the last decades, in pace with surgical and technological advances. A wide variety of publications have shown that as suspected, different aspects of the hole’s structural conformation, assessed by OCT, are associated with anatomical and surgical success in macular hole surgery. The hole’s minimum linear dimension, often referred to its size or minimum diameter, has been shown to correlate with successful surgical repair10. Ip *et al* found that lesions with MLD smaller than 400 µm had a greater chance of surgical closure. Since then, a variety of studies have confirmed the correlation between anatomy and rates of closure; for the MLD and also for other dimensions such as the hole’s inner opening and external base. Out of the basic lesion measurements, the external base diameter has been suggested as the preferred variable to be used due to its association with functional and anatomical success, ease of obtaining and clinical significance15,16. Wakely *et al* found that the MLD, while associated with both anatomical and visual success, had a lower level of discrimination of anatomical closure when compared to BD or inner hole opening, and this last variable was considered to be the hardest one to reliably replicate.15.

In addition to the lesion’s basic measurements, the MHI variable has also been shown to be related to surgical outcomes, and would theoretically represent the anteroposterior traction and retinal hydration involved in macular hole formation. As a ratio, it has the advantage of avoiding the influence of axial length over the transverse measurements.15,16 In our study, the inverted ratio was presented to better illustrate the relationship between the index and closure. All correlations between the variable and closure remain unaffected by this choice of presentation, used to aid visualization when presented in graph form.

Different OCT measurements and indices have been proposed as candidates for preoperative evaluation of macular holes, but have not shown to be advantageous over evaluation of the base diameter and MHI 15,16.

The hypothesis that BD and MHI are related to hole closure is confirmed by our present study. In our analysis, out of the basic measurements, the BD was the one with stronger association with closure. The double diameter index (MLD plus external base) is a new variable suggested by our group that had a positive correlation with MH closure, besides the already established MHI.

The model for surgical success derived from our data suggests a very high chance of hole closure that begins decreasing at 843.8µm by 0.10% for every 1µm increase in the size of the BD. The same model also suggests the double diameter index (External base diameter plus minimum linear diameter) of 1148 um is associated with a 100% rate of macular hole closure, and each increase in 100 µm results in a 5,6% decrease on macular closure rate. The present data also suggests that 50% surgical success is achieved at an inverted MHI of around 3.0, which corresponds to a MHI of 0.33 or a hole whose height is a third of it’s base. Our proposed model also predicts that macular holes with BD smaller than 843 µm have a very high chance of closure following conventional ILM peeling, not warranting additional surgical techniques. Furthermore, the timing of lens management, the patient’s age and duration of symptoms also had no effect on surgical success. This might be partially explained by the difficulty in establishing a clear timing for the beginning of the symptoms in this kind of disease.

The preoperative prediction of macular hole closure may be used by retinal surgeons in different ways. One of the great advantages would be the choice of employing ILM flaps for holes with preoperative measurements poorly correlated with closure, instead of simply peeling the ILM from the posterior pole with the traditional technique. In other words, surgeons could employ an inverted ILM flap technique as the primary intervention based on the chances of closure for each MH case.

Potential limitations of this study are the small sample size and the relatively high chances of surgical success, especially in smaller holes, which may skew the data in this direction. In turn, this makes creating a model that has a representative distribution of outcomes for the different sizes of holes more difficult.

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