The Importance of Anatomic Configuration and Cystic Changes in Macular Hole: Predicting Surgical Success with a Different Approach

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ABSTRACT

Purpose: This study aimed to define a novel metric for the area of the macular hole (MH) and cysts located around the hole using an optical coherence tomography (OCT) device.

Methods: This study was conducted with 58 eyes of 56 patients. The patients were divided into two groups according to anatomic closure after surgery. Using the metrics of macular hole index (MHI), tractional hole index (THI), hole forming factor (HFF), macular hole area (HA), the cystoid space areas in the inner retinal layers (CA), and our novel metric, the cyst hole area index (CHAI) was calculated. The correlation of the CA, the HA, and the CHAI with other indexes were assessed. Receiver operating characteristic (ROC) curves and cut-off values were derived for indexes predicting type 1 or type 2 closures.

Results: The CA showed a strong positive correlation with the base MH size and the maximum MH height ($r = 0.624, p < 0.001$; $r = 0.722, p < 0.001$, respectively). The HA showed a strong positive correlation with basal MH size and minimum MH size ($r = 0.934, p < 0.001$; $r = 0.765, p < 0.001$). The HA showed a moderate positive correlation with maximum MH height ($r = 0.483, p < 0.001$, respectively). CHAI showed a moderate positive correlation with minimum MH size ($r = 0.297, p = 0.02$). CHAI and HA showed a moderate negative correlation with post-operative BCVA ($r = -0.39, p = 0.003$; $r = -0.357, p = 0.006$, respectively). ROC curve analysis showed that MHI (0.823), THI (0.750), and HFF (0.722) predicted type 1 closure and that CHAI (0.769) and HA (0.709) predicted type 2 closures.

Conclusion: MH and our novel index CHAI, which can be calculated without any additional software, could successfully predict type 1 and type 2 closures, respectively.

Introduction

The macular hole (MH) is an anatomic opening formed in the center of the fovea.1 It is a treatable cause of central vision loss, which is more common in older people.2,3 MH is also more common in females and is due to tangential traction of the ILM. Recent studies have determined that posterior vitreous detachment (PVD), which causes anterior-posterior vitreomacular traction, is responsible for MH formation.4–7 Since Kelly and Wendel first managed to close the MH with pars plana vitrectomy (PPV), surgical success has increased up to 75–95% with the development of new techniques.8 The success of the surgery defined by Kang et al. was divided into two groups according to the type of MH closure. Type 1 closure is described as a normal foveal contour without interruption in the foveal tissue continuity above the retinal pigment epithelial layer.9 In type 2 closures, there is an interruption in the continuity of the foveal tissue, and there is no retinal tissue above the retinal pigment epithelial layer.9 The MH margin is thin and attached to the underlying retinal pigment epithelial layer10 (Figure 1).

Various clinicopathological studies have demonstrated the closure of MH centrifugal displacement of photoreceptors from the foveal center, rearrangement of foveal depression, and glial proliferation of Müller cells.11–14 Although a lower disease stage, younger patient age, duration of symptoms, secondary (retinal detachment, myopia, macular telangiectasia, trauma, optic pit), or idiopathic nature, chronicity, vertical metamorphopsia, the experience of the surgeon and the pre-operative visual acuity reflecting the stability of the outer retinal structures are the factors affecting surgical success, understanding the detailed anatomic configuration of MH and clarification through the means of advanced technology will bring a new approach to this issue of which factors have the greatest effect on surgical success.1

Optical coherence tomography (OCT) provides better recognition of MHs and evaluation of foveal structures. Various OCT parameters are typically analyzed to estimate the visual and anatomic outcomes after MH repair. These
metrics include the minimum distance between the MH edges, the maximum diameter at the apex of the MH, the base MH size, and MH height. Various indexes have been developed to estimate the results of these OCT measurements, including hole form factor (HFF), MH index (MHI), and tractional hole index (THI). At the same time, some studies have evaluated the MH area (HA) as well as the cyst areas around MH (CA) by subjecting OCT images to analysis using different software, such as Image J, which has many disadvantages. However, artificial intelligence (AI) now makes it possible for machines to learn from experience, adapt to new inputs, and perform human-like tasks, and has become widely used in medicine. AI has been used for the prediction of accuracy of MH closure based on OCT images.

Histopathological studies of autopsy eyes with MH have shown intraretinal alteration surrounding MH, including cystic retinal edema and deterioration of the photoreceptor layer. However, the effect of cystic changes on the anatomic and functional success of the surgery has not been fully elucidated. In this study, the aforementioned new metrics were measured, including CHAI, with the OCT device without additional software and the effect of MH configuration and cystic alterations on anatomic and functional results was investigated with a different unique perspective.

Materials and methods

This was a retrospective, cross-sectional, single-center case study. The study included 58 eyes of 56 patients who underwent 23-gauge PPV with the diagnosis of idiopathic MH in the ophthalmology clinic of a tertiary level university hospital between 2016 and 2020. The subjects included were those who underwent PPV and internal limiting membrane peeling for idiopathic MH with a minimum of 6 months post-operative follow-up. Exclusion criteria were defined as traumatic MH, the presence of diabetes mellitus or hypertension-induced retinopathy, a history of vitreous surgery or retinal detachment surgery, high myopia (including axial length >26.00 mm or 6.00 D refractive error), uveitis history, any fundus disease other than MH, history of intravitreal injection, or any ocular pathology other than concomitant visually significant cataract.

Relevant clinical and surgical history information was collected. All patients included in the study underwent a comprehensive ophthalmological examination, including best-corrected visual acuity (BCVA), as measured on a Snellen eye chart, recorded pre-operatively and at the last visit, and converted to logarithms of minimum angle resolution (log MAR) acuities, slit-lamp biomicroscopy, dilated fundus examination, and OCT (Heidelberg Spectralis, Heidelberg Engineering, Dossenheim, Germany). Full-thickness MH was defined using the spectral domain OCT criteria in the International Vitreomacular Traction Study. Patients were evaluated in two types of anatomic outcomes at 6 months post-surgery as type 1 and 2 according to Kang et al., as described in the Introduction. This study was performed in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee (2021/216-3405). Informed consent was waived due to the retrospective nature of the study.

Surgical steps

Surgery was performed by the same surgeon (Y.O.) in all cases, using standard 3-port, 23-gauge pars plana vitrectomy. When a cataract was present, a combined phacovitrectomy.
was performed. Twenty-three-gauge trocar cannulas were placed 3.5 mm posterior to the limbus. Patients underwent PPV and internal limiting membrane peeling surgery. The posterior hyaloid was wholly detached from the retina after the core vitrectomy. The brilliant blue injection was applied to visualize the internal limiting membrane in the macular region, and the internal limiting membrane was peeled off. Liquid-air exchange was performed, and the air in the vitreous cavity was replaced with 20% sulfur hexafluoride. After the surgery, patients were advised to stay in the prone position for 1 week.

**OCT measurements**

Spectralis SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was used for OCT imaging. Spectralis SD-OCT incorporates real-time eye-tracking software and has the advantage of improving quality and segmentation accuracy in the macular region. The pre-operative and post-vitrectomy OCT examinations were reviewed. Macular scans and 25 horizontal B scans centered on the fovea were performed. The area to be measured was taken from the 12th or 13th images that exactly centered the macula. The caliper function in the device software was used to take the measurement. Images with an image quality score >20 were used in patients without cataracts. A lower quality score of 15 on pre-operative OCT images was selected for patients with cataracts, and the images with the highest quality score were evaluated.

Basal MH size, minimum MH size, MH height, right and left arm length, CA, and HA were measured on the OCT images using the device’s internal measurement function. According to the measurements, previously reported MHI, HFF, and THI were calculated. MHI was defined as the ratio of the MH height to the MH bottom diameter, and THI was defined as the ratio of the MH height to the narrowest diameter of the MH. HFF was calculated by taking the sum of the lengths of the nasal and temporal arms and dividing it by the longest base diameter of MH. CHAI was found by dividing the HA by CA. Measurements were made at different times by two different observers (YO, NK). The measurement techniques of HA, CA, and HFF are shown in Figures 2 and 3. Each index was measured twice by the observers and averaged. The mean of the two observers’ measurements was then used for statistical analysis. To evaluate the reproducibility of the measurements before analysis, for each measured section, inter-examiner ICC was >0.90 (95% confidence interval 0.90–0.92).

**Statistical analysis**

The data were analyzed using SPSS vn.16.0 software (SPSS Inc., Chicago, IL, USA). Conformity of the variables to normal distribution was investigated using visual (histogram and probability plots) and analytical methods (Kolmogorov–Smirnov test). The Mann–Whitney U test was used to compare median values. Categorical variables were compared with the Chi-square test. Spearman correlation test, anatomic results, and the parameters of basal MH size (µm), minimum MH size (µm), MH height (µm), CA (mm²), and HA (mm²) were used to analyze the correlation between the outcomes. ROC curve analysis was performed to evaluate the predictive ability of the CA, HA, and CHAI. The area under the ROC curve was calculated to evaluate the effectiveness of each parameter. The cut-off value was obtained from the ROC curve, and sensitivity and specificity were determined. A p-value <0.05 was considered statistically significant.

![Figure 2](image-url)
Results

The evaluation was made of 58 eyes of 56 patients, with a mean age of 69.8 ± 6.7 (59–91) years, and a male to female ratio of 22:34. Type 1 closure was defined as a successful closure. As a result of MH surgery, 37 (63.8%) eyes were evaluated as type 1, and 21 (36.2%) as type 2 closures. The mean follow-up duration was 13 ± 2.5 months. The mean pre-operative BCVA was 1.4 ± 0.3 log MAR pre-operatively, and 0.9 ± 0.5 log MAR at the last post-operative follow-up. Post-operative vision increased significantly (p < 0.001). Phacovitrectomy was performed in 16 patients with type 1 closures and nine patients with type 2 closure (Figures 4 and 5). For Type 1 closures, higher area under curve (AUC) values of MHI (0.823), THI (0.750), and HFF (0.722) were recorded. Higher AUC (>0.5) values of HA (0.709) and CHAI (0.769) were recorded for type 2 closures. MH was determined to have 75% sensitivity and 75% specificity in the prediction of type 1 closures. A cut-off value of 2.08 for CHAI was determined to have 77% sensitivity and 73% specificity in the prediction of type 2 closures (Table 3).

Discussion

Recent advances in the visualization of the retina, spearheaded by OCT technology, will likely revolutionize the current management of macular diseases. In this study, the effect of the pre-operative OCT biomarkers on the surgical success of MH was investigated, bringing a new understanding from a different perspective. The anatomic configuration of MH and its elevated edematous arms on biomicroscopic evaluation primarily occur as a result of the severity of anteroposterior and tangential tractional forces compressing the MH. Therefore, the OCT study of MH is based on the architecture of the MH; the ratio of areas engaged by the MH configuration and intraretinal cyst could be significant predictive factors in evaluating the severity of tangential and anteroposterior tractional forces. In a recent study conducted by Joo et al., intraretinal cyst height was reported to be greater in type 1 than type 2 closure. Conversely, intraretinal cyst width, diagonal length, and

Table 1. Macular hole indexes between the two types of macular hole closures were analyzed using the Mann–Whitney U test.

| Variable                  | Type 1 closure | Type 2 closure | p-Value |
|---------------------------|----------------|----------------|---------|
| Pre-operative BCVA (log MAR) | 1.31 ± 0.35    | 1.55 ± 0.38    | 0.01    |
| Post-operative BCVA (log MAR) | 0.65 ± 0.4     | 1.3 ± 0.44     | <0.001* |
| Base MH size (µm)         | 977 ± 342      | 1355 ± 544     | 0.003*  |
| Minimum MH size (µm)      | 400 ± 196      | 599 ± 226      | 0.001*  |
| Maximum hole height (µm)  | 504 ± 107      | 476 ± 177      | 0.04*   |
| HFF                       | 0.84 ± 0.19    | 0.68 ± 0.18    | 0.006*  |
| MHI                       | 0.56 ± 0.20    | 0.39 ± 0.17    | <0.001* |
| THI                       | 1.8 ± 1.6      | 1.02 ± 0.85    | 0.001*  |
| CA (mm²)                  | 0.17 ± 009     | 0.15 ± 0.17    | 0.136   |
| MHA (mm²)                 | 0.29 ± 0.11    | 0.41 ± 0.24    | 0.03*   |
| CHAI                      | 2.07 ± 1.15    | 5.21 ± 5.83    | 0.001*  |

BCVA: best corrected visual acuity; MH: macular hole; HFF: hole forming factor; MHI: macular hole index; THI: tractional hole index; CA: cysts area; HA: hole area; CHAI: cyst hole area index.

m) 400 ± 196 599 ± 226 0.001* 0.5) values of HA (0.709) and CHAI (0.769) were recorded. Higher AUC (>0.5) values of HA (0.709) and CHAI (0.769) were recorded for type 2 closures. MH was determined to have 75% sensitivity and 75% specificity in the prediction of type 1 closures. A cut-off value of 2.08 for CHAI was determined to have 77% sensitivity and 73% specificity in the prediction of type 2 closures (Table 3).

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Figure 3. Measurement technique of HFF (a) temporal arm (b) nasal arm (c) base diameter HFF = (a + b)/c.
BCVA: best corrected visual acuity; MH: macular hole; HFF: hole forming factor; MHI: macular hole index; THI: tractional hole index; CA: cysts area (mm²); HA: hole area (mm²); CHAI: cyst hole area index.

Spearman correlation test.

*Statistically significant.

Table 2. Results of the correlation coefficient between intraretinal cystoid space area, hole area, cyst hole area index, and other pre-operative variables.

| Variable                      | CA   | p-Value | HA   | p-Value | CHAI | p-Value |
|-------------------------------|------|---------|------|---------|------|---------|
| Post-operative BCVA           | 0.124| 0.35    | −0.357| −0.006*| −0.39| 0.003*  |
| Base MH size (µm)             | 0.624| <0.001*| 0.934| <0.001*| 0.05 | 0.93    |
| Minimum MH size (µm)          | 0.252| 0.056   | 0.765| <0.001*| 0.297| 0.02*   |
| Maximum MH height (µm)        | 0.722| <0.001*| 0.483| <0.001*| −0.604|<0.001*  |
| HFF                           | 0.42 | 0.75    | −0.403| 0.002*| −0.361|0.007*   |
| MHI                           | −0.181| 0.17   | −0.673| <0.001*| −0.257|0.058    |
| THI                           | 0.3  | 0.82    | −0.475| <0.001*| −0.389|0.003*   |

BCVA: best corrected visual acuity; MH: macular hole; HFF: hole forming factor; MHI: macular hole index; THI: tractional hole index; CA: cysts area (mm²); HA: hole area (mm²); CHAI: cyst hole area index.

Figure 4. ROC analysis graphics of HFF, THI, and MHI for type 1 closure.

Figure 5. ROC analysis graphics of CA, HA, and CHAI for type 2 closure.

evaluation of the intraretinal cyst, such as width and height, could be a better criterion for anatomic closure and may be able to be used as a basis for prediction.

Hitherto, MHI, THI, and HFF indices have been evaluated in many studies to measure success in MH surgery.\textsuperscript{15,16,18,28,29} MHI and THI represent the effect of putative tangential, anteroposterior vitreomacular traction forces, and retinal hydration on MH development.\textsuperscript{15,16} HFF reflects whether the bilateral detached photoreceptor layer is long enough to cover the exposed RPE layer.\textsuperscript{18} Liu et al.\textsuperscript{28} evaluated MHI, THI, and MHCI (HFF) in 165 eyes of 164 patients with MH. The patients were separated into three groups according to the degree of post-operative anatomic closure. [A (bridge-like closure), B (good closure), and C (poor closure or no closure)]. It was reported that only MHCI (HFF) can predict anatomic success (cut-off value 0.7 for A and 1.00 for B).\textsuperscript{28} However, that study did not specify which stage of MH was evaluated. Moreover, minimum, and basal MH diameters were not investigated, and the correlations of these parameters with these MH diameters are unclear.\textsuperscript{28} In another study, Wakely et al.\textsuperscript{18} evaluated the minimum linear diameter, pre-operative basal diameter MH, MHI, HFF, and THI indices in 50 patients undergoing MH surgery. Similar to the current study, pre-operative basal diameter and minimum linear diameter was found to be associated with anatomic and functional success.\textsuperscript{18} However, since no significant difference could be found for MHI, HFF, and THI, it was stated that these indices presented no real advantage in evaluating anteroposterior and tangential tractions of MH. Only four patients (8%) were operated on for stage 4 MH in that study. In the current series, 28 (48%) patients were operated on for stage 4 MH. Gumus et al.\textsuperscript{51} also showed that minimum linear diameter and basal hole diameter were greater, and reopening was more common in type 2 closure.

Yu et al.\textsuperscript{29} compared these indices in stage 3 and stage 4 MH and showed that HFF and THI were higher in patients with stage 3 MH, but MH was similar between the two groups. However, it was postulated that patients with stage 3 MH had a lower duration of symptoms and smaller MH diameters than those of stage 4, and in cases with MH diameter >400 µm, holes of the two stages were similar in clinical features and morphological parameters. However, the design of the study did not include the effects of these indices on surgical success.\textsuperscript{29} Briefly, the findings of this study showed that greater MHI, THI, and HFF were associated with type 1 closure (reflecting surgical success), especially in stage 4 MH, which is characterized by a larger MH diameter, full separation of posterior vitreous detachment, and maximum effect of anteroposterior and tangential tractions. Moreover, MHI and THI were found to be more sensitive and specific than HFF in predicting type 1 closure. This proves that the force of anteroposterior tractions, which is the cornerstone of the MH pathogenesis, reflects MH height rather than nasal and temporal arm height. Archimedes stated that the moment of force applied to the object is \( M = r \times F \), where \( F \) is the applied force, and \( r \) is the distance of the applied force from the object. The
r-value is highest at the apex of MH. The moment obtained at the apex of MH, which is characterized mainly by the MH height, reaches its maximum. The probability of type 1 closure increases when anteroposterior tractions, which represent MH height, are removed by surgery, and vision reaches the desired maximum level with the resolution of cystic areas.

To the best of our knowledge, the information about the relationship between cystic space and hole area of MH is scarce in the literature. In this study, the novel index CHAI was found to predict type 2 closure with high sensitivity (77%) and specificity (73%) compared to HA (p = 0.001). In addition, CHAI and HA were determined to be negatively correlated with post-operative BCVA. Greater HA indicates that the tractional forces affecting MH are stronger, the stage of MH is advanced, and chronicity, and therefore this situation is related to the lack of benefit from the surgery for the reasons explained. As mentioned above, CHAI is obtained by dividing HA by CA. The critical point of this issue is that a lower CA increased the CHAI, making it a more sensitive and specific index for predicting type 2 closure compared to HA. In this respect, CA may be considered a factor preventing surgical failure. Moreover, CA showed a strong correlation with maximum MH height, which is the most important predictive parameter assumed for type 1 closure (r = 0.722, p < 0.001). Venkatesh et al.32 evaluated various indices in 49 patients with idiopathic full-thickness MH and showed that the MH cystoid space area index, which is obtained by dividing the macular hole cystoid space area by the total area, is predictive of type 1 closure. However, horizontal MH parameters (base MH size, minimum MH size, and maximum MH height) were not evaluated in that study. Furthermore, 20 (41%) of the cases were failed after the first surgery and underwent a second procedure with silicone tamponade or gas. Those results were discussed, ignoring the possible effects of silicone on the retina. In the current study cases, standard MH surgery was applied in parallel with the other studies, and 20% sulfur hexafluoride was used in all cases.

In a recent study, Joo et al.30 investigated the effect of intraretinal cyst specifications (width, height, diagonal length, angle) on predicting MH closure and showed that intraretinal cyst height was greater in type 1 closure compared to those of type 2 closure. These current study results are supported by these studies. In response to retinal injuries or pathologies, there is an activation of Müller cells characterized by reactive gliosis, which is the basis of the pathogenesis of MH closure with hypertrophy, proliferation, and upregulation of glial fibrillary acidic protein (GFAP). Romano et al.33 compared the GFAP immunoreactivity and OCT parameters of idiopathic epiretinal membranes and diabetic epiretinal membranes and found the number of intraretinal cysts and GFAP immunoreactivity in the diabetic epiretinal membrane to be higher than in the idiopathic group. Due to the possible contribution of intraretinal cysts to GFAP production, CA may be thought of as a preventive factor for type 2 closure. The novel index CHAI can be considered to be able to be used with greater differentiation than HA, which is widely known in the literature and is associated with type 2 closure.

AI in medicine is currently being used to search for medical data and uncover insights that will help improve health outcomes and patient experiences and will come with groundbreaking options in the future. Hu et al.21 developed a deep learning model to predict the post-surgical status of idiopathic MH and showed that this model was successful in estimating MH status after the surgery with an AUC of 89.32% (83.30% sensitivity, 87.50% specificity). Xiao et al.23 were also able to predict the post-surgical status of MH with an AUC of 94.0% (95.8% sensitivity, 87.5% specificity) with a machine learning model. In another study conducted by Xiao et al.,22 a hybrid model to predict MH closure was developed including deep learning and multimodal deep fusion network, and it was shown that this hybrid model could predict MH closure with an AUC of 94.7% (97.9% sensitivity, 81.5% specificity). As a result, AI using deep learning on OCT images or machine learning to integrate different MH metrics can be used to predict MH closure with an accuracy higher than single MH metrics alone.21,23 A hybrid model with deep features and MH metrics has even higher accuracy.22

There were some limitations to this study, primarily the retrospective design, relatively small sample size, and that cases could not be evaluated longitudinally. It is also unclear when the changes in intraretinal cystoid spaces and OCT parameters occur and how they progress over time.

**Conclusion**

MHI is the most important biomarker with high sensitivity and specificity in predicting type 1 closure. The novel index, CHAI, is a strong predictor for type 2 closure. Extended evaluation of MH parameters will establish the value of understanding anatomic configuration and cystic changes as an important biomarker for predicting successful closure. Further research with an extended cohort and automated measurements, leveraging the advantage of the developments in machine learning together with a longer follow-up period, is essential to validate these results and assess the value of the biomarkers for understanding the pathophysiology of MH.
Author contributions
Y.O.: concept and design. Y.O., N.K., N.A., A.O.K., and S.K.: data collection or processing. Y.O., A.A., and S.I.: analysis or interpretation. A.A.: literature search. Y.O. and A.A.: writing.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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