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

Yücel Ozturk (✉ yucellozturk@yahoo.com)

Haydarpasa Numune Egitim ve Arastirma Hastanesi: Istanbul Haydarpasa Numune Egitim ve Arastirma Hastanesi <https://orcid.org/0000-0002-8520-0073>

Abdullah Ağın (✉ abdullahagin@gmail.com)

Haseki Training and Research Hospital: Istanbul Haseki Egitim Ve Arastirma Hastanesi
<https://orcid.org/0000-0001-7173-8617>

Nadir Kockar

Haydarpasa Numune Egitim ve Arastirma Hastanesi: Istanbul Haydarpasa Numune Egitim ve Arastirma Hastanesi

Nevzat Ay

Haydarpasa Numune Egitim ve Arastirma Hastanesi: Istanbul Haydarpasa Numune Egitim ve Arastirma Hastanesi

Serhat Imamoglu

Haydarpasa Numune Egitim ve Arastirma Hastanesi: Istanbul Haydarpasa Numune Egitim ve Arastirma Hastanesi

Alev Ozcelik Kose

Haydarpasa Numune Egitim ve Arastirma Hastanesi: Istanbul Haydarpasa Numune Egitim ve Arastirma Hastanesi

Süleyman Kugu

Haydarpasa Numune Egitim ve Arastirma Hastanesi: Istanbul Haydarpasa Numune Egitim ve Arastirma Hastanesi

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Abstract

Purpose

This study aimed to define novel metrics for the area of the macular hole (MH) and the cysts placed around the hole using an optical coherence tomography (OCT) device.

Methods

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

Results

The CA positively correlated with the base MH size and the maximum MH height ($p < 0.001$, $p < 0.001$, respectively). The HA showed a positive correlation with basal MH size, minimum MH size, and maximum MH height ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). CHAI was positively correlated with minimum MH size. ($p = 0.02$). CHAI and HA were negatively correlated with postoperative BCVA ($p = 0.003$, $p = 0.006$, respectively). ROC curve analysis showed that MHI, THI, and HFF predicted type 1 closure; on the other hand, CHAI and HA predicted type 2 closures.

Conclusions

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

Key Messages

MHI, which reflects the height of the macular hole, is the most important biomarker with high sensitivity and specificity in predicting type 1 closure. Our novel index, CHAI, obtained by dividing the macular hole area by the cystoid space areas in the inner retinal layers, is a strong predictor for type 2 closure. The presence of cystoid space areas in the inner retinal layers emerges as a factor preventing Type 2 closure.

Introduction

The macular hole (MH) is an anatomical 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]. Recent studies have determined that posterior vitreous detachment (PVD), which causes anteroposterior vitreomacular traction, is

responsible for MH formation[4-7]. Since Kelly and Wendel managed to close the MH with pars plana vitrectomy (PPV), surgical success has increased remarkably with the new techniques developed up to 75%-95%[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's continuity above the retinal pigment epithelial layer [9]. On the contrary, 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 layer [10].

In various clinicopathological studies, the closure of MH centrifugal displacement of photoreceptors from the foveal center, rearrangement of foveal depression, and glial proliferation of Müller cells has been demonstrated [11-14]. Although, lower disease stage, younger patient, duration of symptoms, secondary (retinal detachment, myopia, macular telangiectasia, trauma, optic pit) or idiopathic nature, its chronicity, vertical metamorphopsia, the experience of the surgeon and the preoperative visual acuity reflecting the stability of the outer retinal structures are the factors affecting the surgical success, understanding the detailed anatomical configuration of MH and its clarification with the help of advanced technology will bring a new approach to this issue which factors are influential on the surgical success[1].

Optical coherence tomography (OCT) provides better recognition of MH's and evaluation of foveal structures. Various OCT parameters are typically analyzed to estimate the visual and anatomical 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)[15-18]. 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 [19,20].

Histopathologic studies of autopsy eyes with MH show intraretinal alteration surrounding MH, including cystic retinal edema and deterioration of the photoreceptor layer[21]. However, the effect of cystic changes on the anatomic and functional success of the surgery is not fully elucidated. In this study, we measured the aforementioned new metrics, including CHAI, with the OCT device without additional software and investigated the effect of MH configuration and cystic alterations on anatomical and functional results with a different unique perspective.

Materials And Methods

This study is a retrospective, cross-sectional, single-center case study. Fifty-eight eyes of 56 patients who underwent 23-gauge PPV with the diagnosis of idiopathic MH in the ophthalmology clinic of the tertiary university hospital between 2016 and 2020 were included in the study. Subjects who underwent PPV and internal limiting membrane peeling for idiopathic MH and a minimum of 6 months of postoperative follow-up were included in this study. Exclusion criteria were traumatic MH's, patients with diabetes

mellitus or hypertension-induced retinopathy, history of vitreous surgery or retinal detachment surgery, high myopia (including axial length greater than 26.00 mm or - 6.00D refractive error), uveitis history, any fundus disease other than MH, history of intravitreal injection, and 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 ophthalmologic examination, including best-corrected visual acuity (BCVA), as measured on a Snellen eye chart, was recorded preoperatively and at the last visit and converted to logarithms of minimum angle resolution (log MAR) acuities, slit-lamp biomicroscopy, dilated fundus examination, and OCT. Full-thickness MH was defined using the spectral domain OCT criteria in the International Vitreomacular Traction Study [20]. After surgery, patients were divided into two types of anatomical outcomes: Type 1, where the MH is entirely closed, and type 2, in which the MH does not close with the absence of the foveal area of the neurosensory retina.

Surgical steps

Surgery was performed using a 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 surgery, patients were advised to stay in the prone position for one 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. OCTs at all visits (before MH formation, during MH formation, and after vitrectomy) 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's software was used in the measurement. Images with an image quality score above 20 were used in patients without cataracts. A lower quality score of 15 was chosen in preoperative OCT images in 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 using the device's internal measurement function in OCT images. 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 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 technique of HA and CA is shown in Figure 1. 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 greater than 0.90 (95% confidence interval 0.90–0.92).

Statistical analysis

The data were analyzed with the SPSS 16.0 (SPSS Inc., Chicago, IL, USA) program. Data distribution was analyzed with the Shapiro-Wilk test. The Mann–Whitney U test was used to compare median values. Spearman correlation test, anatomical result, and different parameters such as basal MH size (μm), minimum MH size (μm), MH height (μm), CA (mm^2), and HA (mm^2) were used to analyze the correlation between the outcomes. A 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.

Results

In the study, which included 58 eyes of 56 patients, the mean age was 69.8 ± 6.7 (59–91) years, and the male to female ratio was 22:34. As a result of MH surgery, 37 (63.8%) eyes were type 1, and 21 (36.2%) patients had type 2 closures. The mean preoperative BCVA was 1.4 ± 0.3 log MAR, while the mean BCVA at the last postoperative follow-up was 0.9 ± 0.5 log MAR. Postoperative vision increased significantly ($p < 0.001$). An examination of the MH staging revealed that 22 (37%) eyes were stage 2, 8 (13%) eyes were stage 3, and 28 (48%) eyes were stage 4.

Postoperative BCVA was 0.65 ± 0.4 log MAR in type 1 closures and 1.3 ± 0.44 log MAR in type 2 closures. Visual acuity increased significantly when anatomical success was achieved in patients ($p < 0.001$). As shown in Table 1, there were statistically significant differences in type 1 closures compared to type 2 closures in OCT measurements, basal MH size, minimum MH size, maximum MH height, HFF, MHI, THI, HA, and CHAI.

As shown in Table 2, the CA showed a positive correlation with base MH size and maximum MH height ($r = 0.624$, $p < 0.001$; $r = 0.722$, $p < 0.001$, respectively). HA was positively correlated with base MH size, minimum MH size, and maximum MH height ($r = 0.934$, $p < 0.001$; $r = 0.765$, $p < 0.001$; $r = 0.483$, $p < 0.001$, respectively). HA were negatively correlated with postoperative BCVA, HFF, MHI, THI ($r = -0.357$, $p = 0.006$; $r = -0.403$, $p = 0.002$; $r = -0.673$, $p < 0.001$; $r = -0.475$, $p < 0.001$ respectively). CHAI was positively correlated with minimum MH size ($r = 0.297$, $p = 0.02$). CHAI was negatively correlated with postoperative BCVA, maximum MH height, HFF, and THI ($r = -0.39$, $p = 0.003$; $r = -0.604$, $p < 0.001$; $r = -0.361$, $p = 0.007$; $r = -0.389$, $p = 0.003$, respectively).

ROC curve analysis revealed that MH indexes, such as MHI, THI, and HFF, successfully predicted type 1 closures, whereas HA and CHAI predicted type 2 closures. (Figure 2-3) For Type 1 closures, higher AUC (>0.5) 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. We found 75% sensitivity and 75% specificity for MHI, frequently used to predict type 1 closures. In predicting type 2 closures, 77% sensitivity and 73% specificity were found for CHAI, with a cut-off value of 2.08 (Table 3).

Discussion

Recent advances in the visualization of the retina spearheaded by OCT technology will likely revolutionize the management of macular diseases today [22-24]. In this study, we investigated the effect of the preoperative OCT biomarkers on the surgical success of MH and brought a new understanding with a different horizon.

Hitherto, MHI, THI and HFF indices have been evaluated in many studies to measure success in MH surgery. [15,16,25,18,26] MHI, THI represents the effect of putative tangential, anteroposterior vitreomacular tractions and retinal hydration on MH development [15,16]. HFF reflects whether the bilateral detached photoreceptor layer is long enough to cover the exposed RPE layer[18]. Liu et al. [25] evaluated MHI, THI, and MHCI (HFF) in 165 eyes of 164 patients with MH. Patients were divided into three according to the degree of postoperative anatomic closure. [A (bridge-like closure), B (good closure), and C (poor closure or no closure)]. It has been reported that only MHCI (HFF) can predict anatomical success (cut-off value 0.7 for A and 1.00 for B) [25]. This 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 [25]. On the other hand, Wakely et al.[18] evaluated the minimum linear diameter, preoperative basal diameter MH, MHI, HFF, and THI indices in 50 patients undergoing MH surgery. Similar to our study, preoperative basal diameter and minimum linear diameter were found to be associated with anatomical and functional success [18]. However, since no significant difference could be found for MHI, HFF, and THI, it was stated that these indices did not have a real advantage in evaluating anteroposterior and tangential tractions of MH. Only four patients (8%) were operated on for stage 4 MH in this study. In our series, the number of patients operated on for stage 4 MH was 28 (48%).

Meanwhile, Yu et al.[26] 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 MHI was similar between the two groups. However, they postulated that patients with stage 3 MH had a lower duration of symptoms and smaller MH diameters than those of stage 4; when it comes to MH with a diameter greater than 400 μm , holes of the two stages were similar in clinical features and morphological parameters, on the other hand, the design of the study did not include the effects of these indices on surgical success. [26]. Briefly, our findings show that greater MHI, THI, and HFF were associated with type 1 closure (reflecting the surgical success), especially in stage 4 MH, which characterized greater MH diameters, full separation of posterior vitreous detachment, and maximum efficacy anteroposterior and tangential tractions. Moreover, MHI and THI

were found to be more sensitive and specific than HFF in predicting type 1 closure. This statement proves that the force of anteroposterior tractions, which is the cornerstone of the MH pathogenesis, symbolizes 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. Type 1 closure chance 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 are scarce in the literature. In our study, we found that our novel index CHAI predicted type 2 closure with high sensitivity (77%) and specificity (73%) compared to those of HA ($p=0.001$). Besides, CHAI and HA have negatively correlated with postoperative BCVA. The fact that greater HA indicates that the tractional forces affecting MH are stronger, the stage of MH is advanced, and chronicity of the case, and this situation is related to the lack of benefit from the surgery for obvious reasons explained as expected. As mentioned above, CHAI is obtained by dividing HA by CA. The critical point on this issue is the lower CA increased the CHAI, making it a more sensitive and specific index for predicting type 2 closure compared to HA. From this point of view, CA may be considered as a factor preventing surgical failure. Additionally, CA shows a high correlation with maximum MH height, which is the most important predictive parameter which we supposed for type 1 closure ($r=0.722$, $p<0.001$). Venkatesh et al.

[27] 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 for type 1 closure. However, horizontal MH parameters (base MH size, minimum MH size, and maximum MH height) were not evaluated in this study. Furthermore, 20 (41%) of the cases were failed after the first surgery and underwent a second procedure with silicone tamponade or gas. These results were discussed, ignoring the possible effects of silicone on the retina. In our cases, standard MH surgery procedure was applied in parallel with the other studies, and 20% sulfur hexafluoride was used in all cases.

In a recent study conducted by Joo et al. [28] 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. Our results are supported by these studies. In response to retinal injuries or pathologies, there is an activation of Muller 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. [29] compared the GFAP immunoreactivity and OCT parameters of idiopathic epiretinal membranes and diabetic epiretinal membranes. They found the number of intraretinal cysts and GFAP immunoreactivity in the diabetic epiretinal membrane to be higher than those of 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. We think that our novel index CHAI can be used more distinctive than HA, which is widely known in the literature and is associated with type 2 closure.

ImageJ program, which has many disadvantages, is widely used for image processing. Image processing requires a complex multi-step procedure. In addition, the use of different software for these measurements causes loss of both personnel, time in the transfer and evaluation of OCT images. Such losses are avoided by using the tools already installed in the OCT program. Meanwhile, in order for OCT images to be evaluated optimally in different programs, the resolutions must be adjusted correctly. In our study, measurements were calculated directly using the own module of the OCT device without using any program.

There are some limitations, including retrospective nature, relatively small sample size, and the cases could not be evaluated longitudinally. Besides, it is 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. Our novel index, CHAI is a strong predictor for type 2 closure. Extended evaluation 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 advancement of machine learning concurrently with a prolonged follow-up, are essential to validate our results and assess the value of the biomarkers for understanding the pathophysiology of MH.

Declarations

Compliance with ethical standards

Funding

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This study protocol was approved by Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee (2021/216-3405)

Informed consent

Informed consent was waived due to the retrospective nature of this study.

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Tables

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

Variable	Type 1 closure	Type 2 closure	p value
Preoperative BCVA (log MAR)	1.31 ± 0.35	1.55 ± 0.38	0.01
Postoperative 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 (mm ²)	0.17 ± 0.09	0.15 ± 0.17	0.136
MHA (mm ²)	0.29 ± 0.11	0.41 ± 0.24	0.03*
CHAI	2.07 ± 1.15	5.21 ± 5.83	0.001*

Mann-Whitney U test, *statistically significant, 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

Table 2. Results of correlation coefficient between intraretinal cystoid space area, hole area and cyst hole area index and other preoperative variables.

Variable	CA		HA		CHAI	
	r	p value	r	p value	r	p value
Postoperative 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*

Spearman correlation test,*statistically significant, 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

Table 3. ROC analysis values for HFF, THI, MHI, CA, HA, CHAI

Variable	AUROC	Cut-off value	Sensitivity (%)	Specificity (%)	P
Tip 1 closure					
HFF	0.722	0.742	64	60	0.006*
MHI	0.823	0.436	75	75	0.000*
THI	0.750	0.984	73	65	0.002*
Tip 2 Closure					
CA	0.445	0.135	62	37	0.513
HA	0.709	0.305	77	56	0.012*
CHAI	0.769	2.08	77	73	0.001*

*statistically significant, HFF=Hole forming factor, MHI=Macular hole index, THI=Tractional hole index, CA=Cysts area, HA= Hole area, CHAI= Cyst hole area index

Figures

Figure 1

Preoperative OCT image (a) area of the cysts around the hole (CA) and (b) the area of the hole (HA)

Figure 2

ROC analysis graphics of HFF, THI, MHI for type 1 closure

Figure 3

ROC analysis graphics of CA, HA, CHAI for type 2 closure