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Measurement of the Macular Hole Diameter by En Face Slab Optical Coherence Tomography Reflectance Imaging

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Purpose: To evaluate the repeatability of macular hole (MH) diameter measurement on en face slab optical coherence tomography (OCT) reflectance images and assess its potential to predict visual acuity (VA).

Methods: We enrolled 27 eyes with full-thickness MHs in this study. Preoperative en face slab OCT reflectance images were obtained. Image binarization, ellipse approximation, and uncorrected measurement of minimum diameter, min(ef_uc), and maximum diameter, max(ef_uc), were performed using ImageJ. In addition, magnification-corrected diameters were calculated as min(ef) and max(ef) using the Littman and modified Bennett formulas. Spectral-domain OCT horizontal images were used as the conventional method for the analysis: min(conv) and max(conv). The inter-rater reliability of the method was evaluated by calculating the intraclass correlation coefficient (ICC). The following relationships were analyzed: (1) between logMAR VA and min(ef_uc), min(ef), and min(conv); and (2) between logMAR VA and max(ef_uc), max(ef), and max(conv).

Results: The min(ef) and max(ef) values were 439.4 ± 240.5 μm and 720.7 ± 346.1 μm, respectively. The ICC values were 0.985 and 0.999 for min(ef) and max(ef), and 0.885 and 0.909 for min(conv) and max(conv), respectively. Multivariate analysis suggested that min(ef), but not min(ef_uc) or min(conv), was associated with pre- and postoperative logMAR VA. Furthermore, max(ef), but not max(ef_uc) or max(conv), was also closely correlated with pre- and postoperative logMAR VA.

Conclusions: The MH diameter measured by our method is highly reproducible and closely associated with VA compared to that measured by the conventional method.

Translational Relevance: The MH diameter measured by this modality might serve as an accurate biomarker to predict visual function in eyes with MH.

Introduction

Full-thickness macular hole (MH) is one of the vitreoretinal disorders that is responsible for poor central vision in the elderly. Pars plana vitrectomy and internal limiting membrane (ILM) peeling for MH have been reported to improve the visual outcomes.[1,2] More recently, the inverted ILM flap technique and autologous retinal transplantation have also been reported to be effective for refractory or large MHs.[3,4] Previous reports suggest that spontaneous resolution of MH occurs in 4% to 6% of cases and that MHs measuring less than 400-μm minimum diameter could show spontaneous closure.[5,6] In addition to the preoperative visual acuity (VA) and stage of MH, the diameter of

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MH has been reported as a critical factor influencing the postoperative visual outcomes.[7–9]

There are two major methods for macular hole size measurements. The first method uses horizontal linear or radial-line B-scan images passing through the fovea obtained by spectral-domain optical coherence tomography (OCT). However, this method presents some problems with respect to precise measurement of the MH diameter. First, it is difficult to identify the exact position of the fovea in some eyes with MHs. Furthermore, patients with MHs have poor central fixation, and a central horizontal scan may not exactly cross the foveal center, resulting in inaccurate measurement, especially when the scan density is sparse. Second, the same B-scan image is usually used for measurement of the minimum diameter as well as the maximum diameter; however, it remains unclear whether or not the minimum diameter and the maximum diameter line up coaxially.

The second method uses en face images. For example, Philippakis et al.[10] recently proposed a novel automated method for measuring the MH diameter on en face OCT images. However, in this previous research, the axial length (AL) and magnification of the OCT images were not taken into consideration in the measurement of the MH diameter. Variability of the AL results in differences in the degree of magnification of OCT or OCT angiography images. Without magnification correction with AL, measurement may deviate up to 20%.[11]

As such, we hypothesized that a more reproducible and accurate method for measuring MH diameter using en face slab OCT reflectance imaging, with incorporation of correction for the AL, might help in more precise prediction of the visual outcomes in eyes with MH. In the present study, we attempted to investigate the minimum and maximum diameters of MHs on en face slab OCT reflectance images and examined its repeatability. We also evaluated differences in the MH diameters between our novel measurement method and the conventional reference method and analyzed the axes of the minimum and maximum diameters. Finally, we investigated the association between pre- and postoperative VA and the MH size measurements obtained with en face slab OCT reflectance imaging and horizontal line scans.

Methods

We enrolled patients with full-thickness MH (FTMH) in this study. The present study enrolled 31 MH eyes that underwent CIRRUS 6000 OCT (Carl Zeiss Meditec, Jena, Germany) measurement between January 1, 2020, and December 31, 2021, in our hospital. Four eyes were excluded due to poor-quality OCT images. Other exclusion criteria were eyes with (1) other retinal diseases, such as diabetic retinopathy; and (2) a history of vitreoretinal surgery. All of the procedures used in the study were in compliance with the tenets of the Declaration of Helsinki. The study was conducted with the approval of the Ethics Committee of Yokohama City University. Informed consent was obtained from each of the participants.

Optical Coherence Tomography

In the present study, we measured the minimum diameter, min(ef_uc), where ef represents en face and uc represents uncorrected; maximum diameter, max(ef_uc); and minimum and maximum magnification-corrected diameters, min(ef) and max(ef), using CIRRUS 6000 OCT en face imaging. Values for min(conv) and max(conv), where conv represents conventional, were obtained using spectral-domain OCT horizontal imaging. En face slab OCT reflectance images (3 × 3 mm) were obtained with the CIRRUS 6000 HD OCT system. Image binarization, ellipse approximation, and measurement of the uncorrected minimum diameter, min(ef_uc), and the maximum diameter, max(ef_uc), were performed using ImageJ (National Institutes of Health, Bethesda, MD) (Fig. 1).

Each en face slab OCT reflectance images were converted to 8-bit images and binarized using the Sauvola method. The hyporeflective area corresponding to MH was converted to the black area. Then, the MH shape was approximated to an ellipse, and the minor and major diameters were measured. In addition, the axis of the major diameter was also measured in each image. For eyes with stage 3 and stage 4 MHs, the minor diameter in the superficial layer was designated as the minimum diameter, min(ef_uc), and the major diameter in the retinal avascular layer was designated as the maximum diameter, max(ef_uc). For eyes with stage 2 MHs, the minor diameter in the retinal deep layer was designated as min(ef_uc), because the pseudo-operculum reduced the quality of the binarized images in the retinal superficial layer. In addition, magnification-corrected diameters of the MHs were calculated as min(ef) and max(ef) using the Littman and modified Bennett formulas:[12,13]

$$t = p \times q \times s$$

where t represents the actual minimum and maximum diameters, min(ef) and max(ef), respectively; p represents a constant for the camera of the imaging system (3.480 for the CIRRUS 6000 HD OCT system); q is the ocular magnification factor (0.01306 × [AL (mm) – 1.82]); and s represents the uncorrected minimum

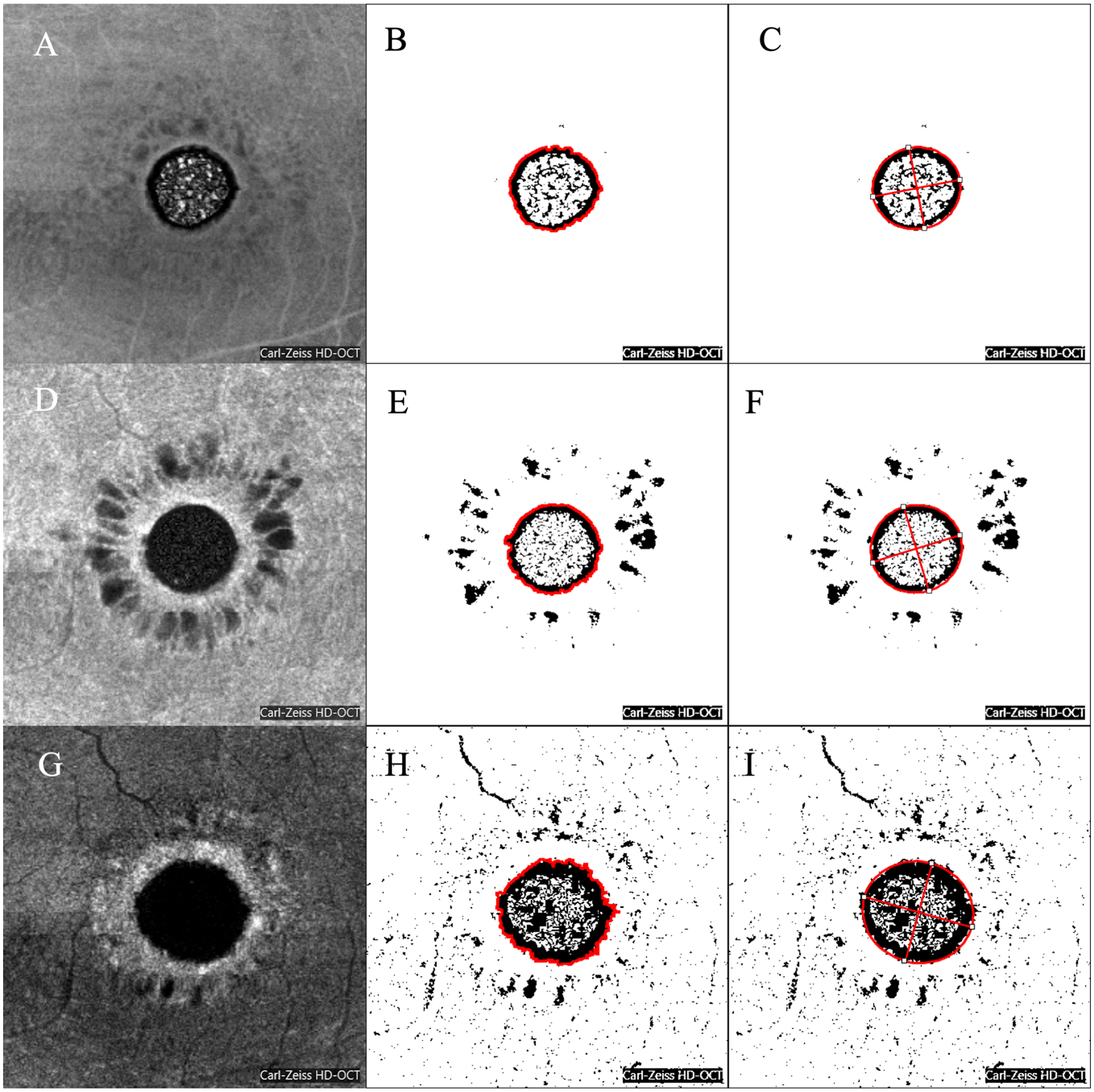

Figure 1. Measurements of the MH diameters on 3 × 3-mm en face slab OCT images. En face slab OCT reflectance images were obtained from the retinal superficial layer (A), retinal deep layer (D), and retinal avascular layer (G) for each eye. The images were binarized using the Sauvola method and ImageJ (B, E, H). The MH shape was then approximated to an ellipse (*red line*), and the minor and major diameters were measured (C, F, I). In the eyes with stage 3 and stage 4 MHs, the minor diameter in the superficial layer was measured as the minimum diameter, min(ef_uc); the major diameter in the retinal avascular layer was measured as the maximum diameter, max(ef_uc). In the eyes with stage 2 MHs, the minor diameter in the retinal deep layer was measured as min(ef_uc).

and maximum diameters, min(ef_uc) and max(ef_uc), respectively.

For measurement of the MH sizes by the conventional method, horizontal images were obtained using SPECTRALIS spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany). The minimum and maximum diameters of the MHs were measured and denoted as min(conv) and max(conv), respectively. For additional assessments, radial-line scans were also used to measure the MH size for the comparison. The axis angle of the major diameter of the approximated ellipse in the superficial layer was measured as A1 and that in the retinal avascular layer as A2.

Statistical Analysis

The inter-rater reliability of the method was evaluated by calculating the intraclass correlation coefficient (ICC). To investigate the inter-rater agreement, two independent investigators (KN and YU) measured min(ef_uc) and max(ef_uc) in each eye. Furthermore, min(conv) and max(conv) were also measured for the analysis. To evaluate the degree of agreement between our current method of measurement of the minimum and maximum MH diameters and the conventional method, we constructed Bland–Altman plots for min(ef) and min(conv) and for max(ef) and max(conv).

The relationships between (1) preoperative logMAR VA (preoperative VA) and min(ef_uc), min(ef), and min(conv); and (2) preoperative VA and max(ef_uc), max(ef), and max(conv) were investigated by multivariate analysis, followed by model selection using the second-order bias-corrected Akaike information criterion (AICc) index. The AIC is an established statistical measure used to evaluate relationships among variables, and it provides an accurate estimate even when the sample size is small.[14,15] Moreover, the relationships between (1) postoperative VA and min(ef_uc), min(ef), and min(conv); and (2) postoperative VA and max(ef_uc), max(ef), and max(conv) were also investigated in eyes that had undergone vitrectomy surgery. All statistical analyses were performed using the R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Demographics

The patient demographic data are shown in the Table. Twenty-seven eyes of 27 patients (10 male and 17 female) with MHs were enrolled in the present study. The mean (±SD) age of the participants was 67.0 ± 8.8 years. Six eyes were diagnosed as stage 2 MH, 11 eyes as stage 3 MH, and 10 eyes as stage 4 MH. Out of 27 enrolled eyes, 26 eyes underwent vitrectomy, and one patient refused surgical treatment. ILM peeling was performed in 23 eyes and the autologous retinal transplantation technique was applied to the remaining three eyes. As a result, all operated eyes showed MH closure and VA significantly improved from 0.649 ± 0.352 to 0.300 ± 0.379 ($P < 0.0001$, Wilcoxon signed-rank test).

Table. Demographic Data

Variable	
Eyes, *n*	27
Male/female, *n*	10/17
Age (y), mean ± SD	67.0 ± 8.8
VA (logMAR), mean ± SD	0.63 ± 0.35
AL (mm), mean ± SD	25.1 ± 2.6
min(ef_uc) (µm), mean ± SD	422.8 ± 232.6
max(ef_uc) (µm), mean ± SD	687.7 ± 320.0
min(ef) (µm), mean ± SD	439.4 ± 240.5
max(ef) (µm), mean ± SD	720.7 ± 346.1
min(conv) (µm), mean ± SD	411.3 ± 268.3
max(conv) (µm), mean ± SD	871.1 ± 296.3
A1, mean ± SD	8.7 ± 34.1
A2, mean ± SD	−0.1 ± 28.1

MH Size Measurements With En Face Slab OCT Reflectance Imaging Showed High Repeatability

We first measured min(ef_uc), max(ef_uc), min(ef), and max(ef) using the CIRRUS OCT en face images and min(conv) and max(conv) using spectral-domain OCT horizontal images, and we compared the ICC values for each parameter. The values of min(ef_uc) and max(ef_uc) were 422.8 ± 232.6 µm and 687.7 ± 320.0 µm, respectively. The ICC value for min(ef_uc) was 0.985 (95% confidence interval [CI], 0.968–0.993) and that for max(ef_uc) was 0.999 (95% CI, 0.993–0.999). After correction for the magnification effect, min(ef) and max(ef) were 439.4 ± 240.5 µm and 720.7 ± 346.1 µm, respectively. For obvious reasons, the ICC values for min(ef) and max(ef) were the same as those for min(ef-uc) and max(ef-uc). The min(conv) and max(conv) measured by the conventional method were 411.3 ± 268.3 µm and 871.1 ± 296.3 µm, respectively. The ICC value for min(conv) was 0.885 (95% CI, 0.763–0.946) and that for max(conv) was 0.909 (95% CI, 0.807–0.958).

Comparison of MH Size Measurements Between En Face Slab OCT Reflectance Images and Horizontal Line Scans

When the measurements with en face slab OCT reflectance images and horizontal lines scans were compared, strong associations of min(ef) with min(conv) ($P < 0.0001$) and of max(ef) with max(conv) ($P < 0.0001$, linear regression analysis) were observed.

Bland–Altman plots are shown in Figures 2A and 2B. The mean of min(ef) and min(conv) was not correlated with the difference between min(ef) and min(conv) ($P = 0.17$). Similarly, the mean of max(ef) and max(conv) was not correlated with the difference between max(ef) and max(conv) ($P = 0.080$). There was a tendency for max(ef) to be smaller than max(conv). Bland–Altman plots demonstrated two outliers in Figures 2A and 2B. Of these four eyes, three

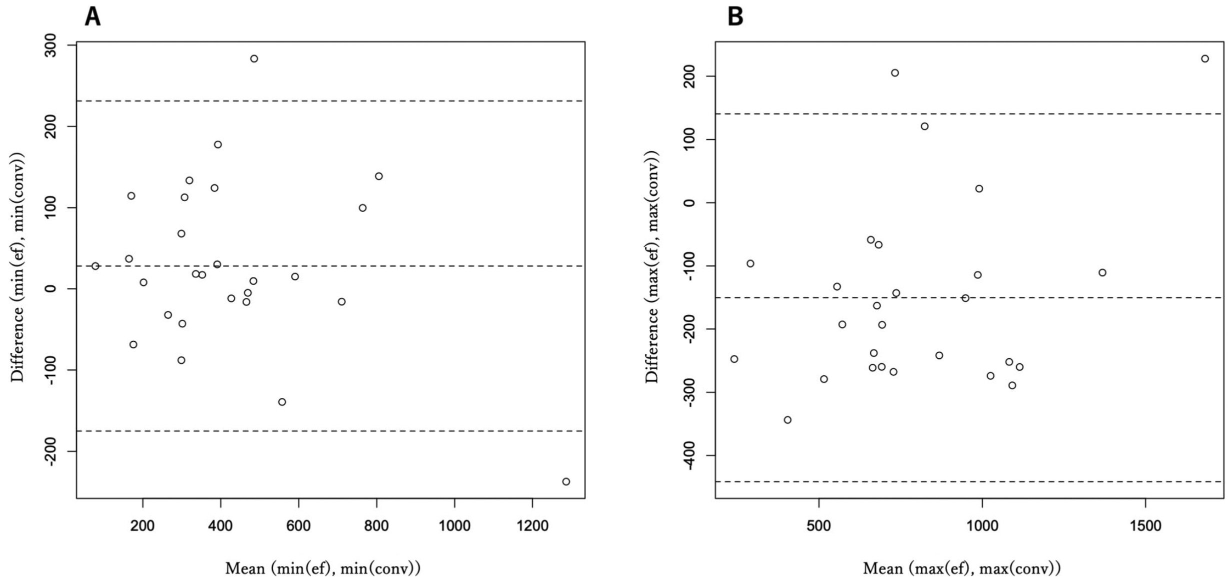

Figure 2. Bland–Altman plots for the two methods of measurement of MH diameter. (A) The *x*-axis shows the average minimum MH diameter measured by the conventional method and our novel method, and the *y*-axis shows the difference in the minimum MH diameters measured by the two measurement methods. (B) The *x*-axis shows the average maximum MH diameter measured by the conventional method and our current method, and the *y*-axis shows the difference in the maximum MH diameter measured by the two measurement methods.

eyes had very high myopia (AL > 30 mm) (Fig. 3), and the AL of the fourth eye was 22.99 mm.

Next, we compared the axis angle of the major diameter of the approximated ellipse in the superficial layer (A1) and that in the retinal avascular layer (A2), which demonstrated that the median A1 and A2 values were 4.4 (interquartile range [IQR], –18.4 to 22.8) and 1.7 (IQR, –13.5 to 12.0), respectively. The difference between A1 and A2 was 6.70 (IQR, 3.20–16.05), which was not statistically significant (P = 0.52, Wilcoxon signed-rank test).

Measurements Using En Face Slab OCT Reflectance Imaging Better Predicted Pre- and Postoperative VA Than Measurements with Horizontal Line Scans

Furthermore, we identified factors predicting pre- and postoperative VA. Univariate analysis showed that min(ef_uc), min(ef), and min(conv) were significantly associated with preoperative VA ($r = 0.652$, $P = 0.00023$; $r = 0.672$, $P = 0.00012$; and $r = 0.598$, $p = 0.0010$, respectively; linear regression analysis). After the AICc model selection, the optimal model for preoperative VA included only min(ef), but not min(ef_uc) or min(conv) (Fig. 4A):

$$\text{Preoperative VA} = 0.191 + 0.0010\ (\pm 0.00022) \times \text{min(ef)}\ (\text{AICc} = 10.9)$$

Univariate analysis identified max(ef_uc), max(ef), and max(conv) as being significantly associated with preoperative VA ($r = 0.646$, $P = 0.00027$; $r = 0.648$, $P = 0.00026$; and $r = 0.580$, $P = 0.0015$, respectively; linear regression analysis). Among max(ef_uc), max(ef), and max(conv), the optimal model for preoperative VA included only max(ef) (Fig. 4B):

$$\text{Preoperative VA} = 0.148 + 0.00067\ (\pm 0.00016) \times \text{max(ef)}\ (\text{AICc} = 12.4)$$

Similar results were obtained for postoperative VA. Univariate analysis suggested that min(ef_uc), min(ef), and min(conv) were significantly associated with postoperative VA ($r = 0.618$, $P = 0.00077$; $r = 0.673$, $P = 0.00016$; and $r = 0.639$, $P = 0.00044$, respectively; linear regression analysis). The optimal model for postoperative VA included only min(ef), but not min(ef_uc) and min(conv) (Fig. 4C):

$$\text{Postoperative VA} = -0.156 + 0.0010\ (\pm 0.00023) \times \text{min(ef)}\ (\text{AICc} = 13.7)$$

On the other hand, univariate analysis suggested that max(ef_uc), max(ef), and max(conv) were significantly associated with postoperative VA ($r = 0.633$, $P = 0.00053$; $r = 0.670$, $P = 0.00018$; and $r = 0.534$, $P = 0.0050$, respectively; linear regression analysis). Among max(ef_uc), max(ef), and max(conv), the optimal model for postoperative VA included only

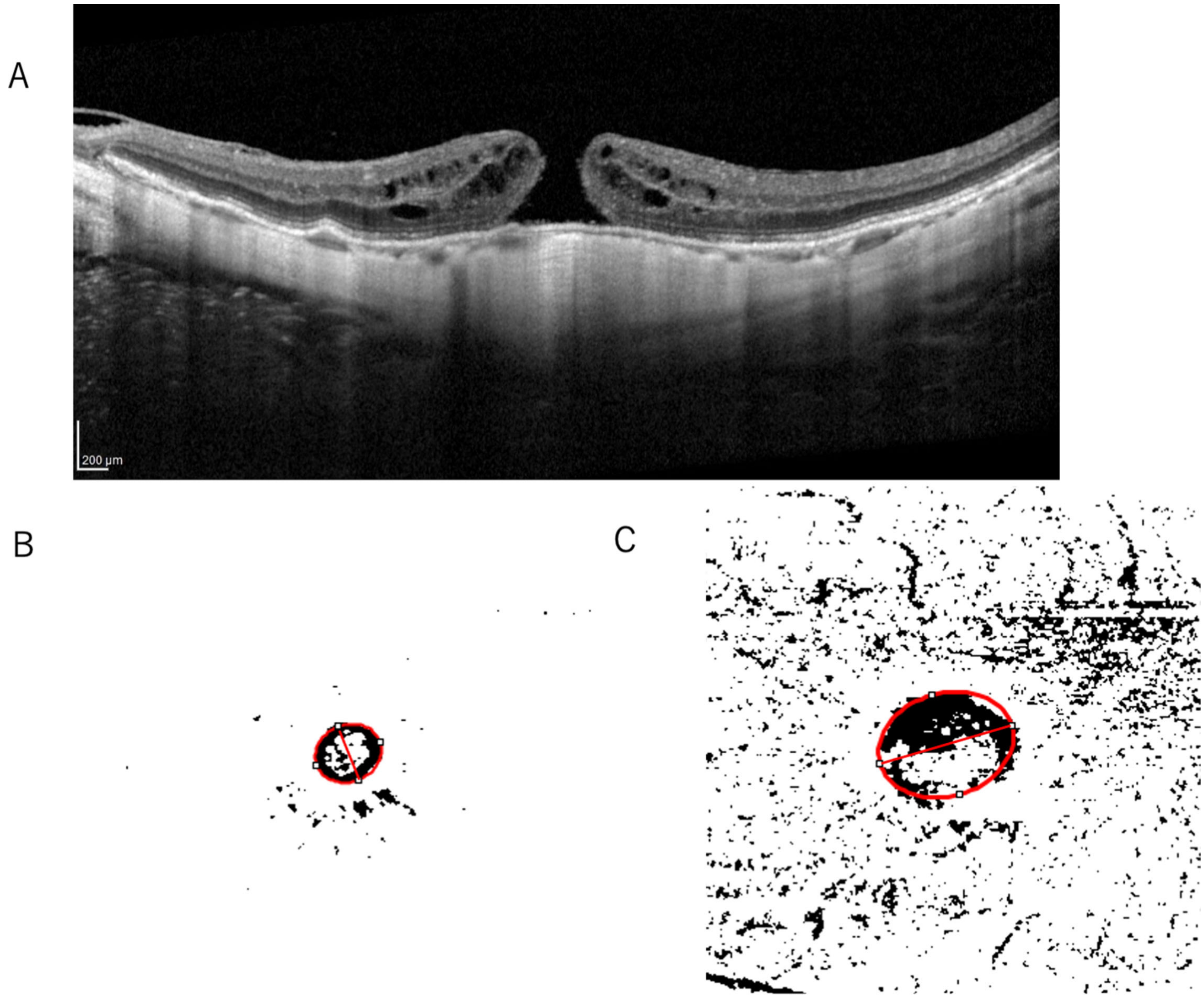

Figure 3. Representative MH case (75-year-old female) that demonstrated the discrepancy in MH diameters. Her left eye was diagnosed as stage 3 MH, and the axial length was 30.45 mm. The logMAR VA improved from 0.699 to 0.523 after vitrectomy surgery. In the conventional method, the minimum diameter, min(conv), was 265 µm; the maximum diameter, max(conv), was 630 µm (A). In our current method, the minimum diameter with magnification correction, min(ef), was 333.1 µm (B), and the maximum diameter with magnification correction, max(ef), was 835.4 µm.

max(ef) (Fig. 4D):

$$\text{Postoperative VA} = -0.217 + 0.00072\ (\pm 0.00016) \times \max(\text{ef})\ (\text{AICc} = 13.9)$$

Measurements Using En Face Slab OCT Reflectance Imaging Better Predicted Pre- and Postoperative VA Than Measurements Using Radial Line Scans

Finally, we measured radial scans with SPECTRALIS OCT for each eye, and the minimum and maximum diameters were calculated. Consequently, the minimum diameter was found to be 339.7 ± 248.0 µm, which was significantly smaller than min(conv) ($P < 0.0001$), and the maximum diameter was 903.7 ± 325.3 µm, which was significantly larger than max(conv) ($P = 0.045$, Wilcoxon signed-rank test). However, the AICc model selection suggested that, among min(ef), min(ef_uc), and modified min(conv), the optimal model for preoperative VA included only min(ef). The optimal model for postoperative VA also included only max(ef) among max(ef), max(ef_uc), and modified max(conv).

Discussion

In the current article, we have proposed a novel method for measuring MH diameter on en face slab

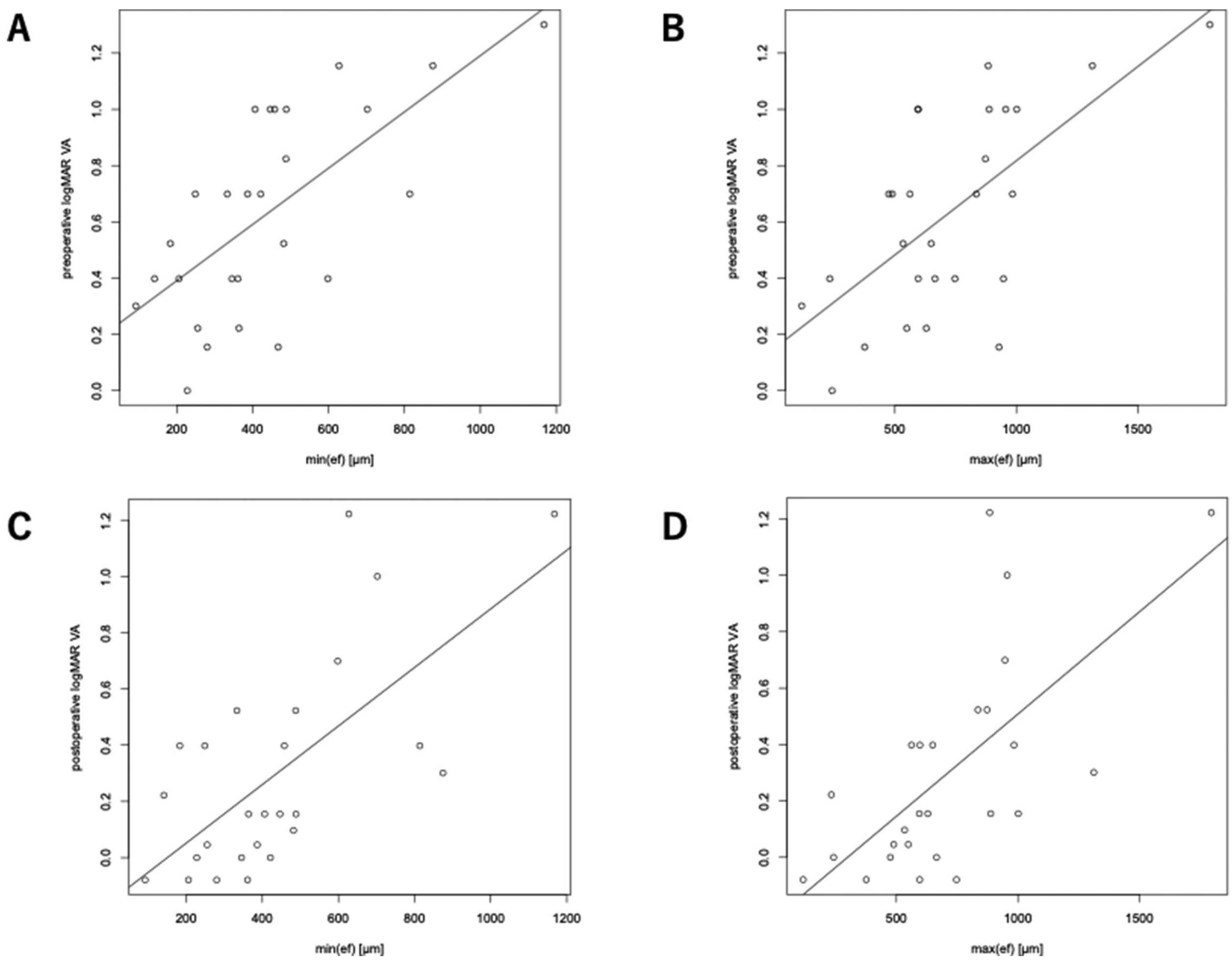

Figure 4. Relationship between the magnification-corrected MH diameters and pre- and postoperative VA. There was a significant relationship between (A) min(ef) and preoperative logMAR VA ($r = 0.672$, $P = 0.00012$), and (B) max(ef) and preoperative logMAR VA ($r = 0.648$, $P = 0.00026$). Significant associations were also seen between (C) min(ef) and postoperative logMAR VA ($r = 0.673$, $P = 0.00016$) and (D) max(ef) and postoperative logMAR VA ($r = 0.670$, $P = 0.00018$).

OCT reflectance images. Our automatic measurement method demonstrated a high inter-rater agreement. No significant systematic error was observed between the present method and the conventional method. The optimal model for pre- and postoperative VA included min(ef) but not min(ef_uc) or min(conv). Similarly, the optimal model for pre- and postoperative VA included max(ef) but not max(ef_uc) or max(conv). Taken together, our current method for measuring MH diameter might be more useful in clinical settings compared with the conventional method.

A recent report by Philippakis et al.[10] proposed an automated method for measuring MH diameter on en face OCT images; in this method, the area of the MH is automatically measured, and the mean diameter is calculated for each eye. Therefore, theoretically, there is no significant difference in mean MH diameters measured by their automated method and those by the conventional method. Consistent with the previous report, the ICC values for the minimum and maximum diameters measured by our current method were higher (0.985 and 0.999, respectively) compared with those for the diameters measured by the conventional method (0.885 and 0.909, respectively), indicating the high reproducibility of our method of measurement on en face slab OCT reflectance images. The current results support the previous study and indicate that measurement on en face OCT images eliminates the potential bias in the conventional manual method of measurement on B-scans.

The conventional manual method of measurement of the minimum and maximum diameters of MHs using B-mode line scans has several limitations. First, it is sometimes difficult to identify the exact foveal position on horizontal OCT B-scan in eyes with a MHs. In clinical settings, the horizontal OCT B-scan passing through the foveal center is considered to be identical to the scan passing across the largest MH width, and experienced graders measure the width with a built-in measurement tool. Indeed, the ICC values were lower compared to measurement method on en face OCT C-scans; the results suggest that the reliability of the conventional method depends on the examiner's experience. In comparison, our measurement method on en face OCT C-scans allows objective assessment of the shape of the MH in each layer (retinal superficial and deep layers and retinal avascular layer) and is therefore more reliable as compared to the conventional method. Additionally, the current study results suggest that the axes of the minimum and maximum diameters are not identical. Specifically, the axis of the major diameter was within 30° in 21 eyes (77.8%), suggesting that the axis of the minimum MH diameter is vertical, whereas the axis of the maximal MH diameter is horizontal in most examined eyes. Both the minimum and maximum diameters have been measured on the same horizontal OCT B-scans passing through the fovea in most studies,[5,6] and it is possible that such simultaneous measurements are not accurate for predicting the functional outcomes in eyes with MHs. Moreover, the magnification-corrected MH diameters were more strongly associated with pre- and postoperative VA as compared with the diameters measured by the conventional method, suggesting that the MH diameter measured on en face slab OCT images might be more representative of the true MH diameter.

Stages in the development of a MH were first described by Gass[16] and recently reclassified by the International Vitreomacular Traction Study Group based on OCT imaging.[17] In the latter OCT-based stage classification, MH diameter is taken into consideration because previous studies have suggested that MH diameter is predictive of the anatomical outcomes after medical/surgical treatment.[18–20] The authors classified FTMH into small FTMH (≤250 μm), intermediate-sized FTMH (>250 μm but ≤400 μm), and large FTMH (>400 μm), according to the conventional method. In the eyes enrolled in our current study, the FTMHs measured by the conventional method were small in five eyes, intermediate-sized in 12 eyes, and large in 10 eyes; in contrast, when classified according to our current measurement method, the FTMHs were small in six eyes, intermediate-sized in seven eyes, and large in 14 eyes. As mentioned previously, the magnification-corrected MH diameters measured in the present study were more strongly associated with pre- and postoperative VA than the MH diameters measured by the conventional method. As such, it appears that the method of measurement described in the present study may better reflect the true MH size compared to the conventional method. We believe that special attention should be paid to highly myopic eyes, as three eyes among four outliers in the Bland–Altman plots were highly myopic eyes.

There are several limitations to the current study. First, we did not have data for "true" MH size. In vivo measurements of MH diameter, using a scale during vitrectomy, would be required to obtain real measurements. Second, the axial length measurement should be performed for the magnification correction in our current method; however, it is not always obtained in MH cases. Finally, automated segmentation of the superficial retinal layer in the stage 2 MH was prone to errors with the current CIRRUS OCT system. As such, deep retinal layer slabs were used for the minimal diameter measurements. However, even with the use of B-scan images, correct measurements of minimum diameters for stage 2 MH are impossible.

In summary, measurement of the MH diameter on en face slab OCT reflectance images, as described in our current study, appears to be a reliable method. The MH diameter corrected for the magnification effect was more strongly correlated with the pre- and postoperative visual function than the other measured parameters. Our current method could be more useful if adopted as an automated algorithm into an OCT system, although AL measurement should be performed for magnification correction. It is possible that further clinical trials with larger sample sizes might clarify the usefulness of our measurement method for predicting the visual outcomes after surgical treatment of MH.

Acknowledgments

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[*] YU and KN contributed equally to this work.

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