tvst

Article

# Defining a Cutoff for Progression of Macular Holes

**Carmen Baumann[1], Saskia Hoffmann[1], Ahmed Almarzooqi[1], Navid Johannigmann-Malek[1], Chris P. Lohmann[1], and Stephen B. Kaye[2]**

[1] Ophthalmology Department, Hospital rechts der Isar, Technical University of Munich (TUM), Munich, Germany
[2] University of Liverpool, William Henry Duncan Building, Liverpool, UK

**Correspondence:** Stephen Kaye, University of Liverpool, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, United Kingdom.
e-mail: s.b.kaye@liverpool.ac.uk

**Received:** June 26, 2021
**Accepted:** September 26, 2021
**Published:** November 2, 2021

**Keywords:** macular hole; size progression; optical coherence tomography (OCT)

**Citation:** Baumann C, Hoffmann S, Almarzooqi A, Johannigmann-Malek N, Lohmann CP, Kaye SB. Defining a cutoff for progression of macular holes. Transl Vis Sci Technol. 2021;10(13):2, https://doi.org/10.1167/tvst.10.13.2

**Purpose:** The purpose of this study was to determine a cutoff for progression of idiopathic full-thickness macular hole (MH) size.

**Methods:** Retrospective analysis of consecutive patients waiting 4 weeks for MH surgery. Two observers performed 3 repeat sets of MH size measurements on optical coherence tomography (OCT) high-density radial scans taken at first presentation and 4 weeks later before surgery. Primary outcome was the definition of a cutoff for true enlargement of MH size versus measurement error. Secondary outcomes were risk factors for change in minimum linear diameter (MLD) size and best-corrected visual acuity (BCVA).

**Results:** Fifty-one patients were included with a mean MH size of 334 µm (±179 µm; range 39 to 793 µm). The cutoff for an increase in MLD size calculated as the outer confidence limit for the 99.73% limits of agreement was 31 µm. This was independent of MH size. Using this cutoff, MLD size increased in 9/34 (26.5%) of patients without and in 14 of 17 (82.4%) of patients with vitreomacular traction (VMT; $P < 0.001$). Mean BCVA deteriorated in patients in whom the MH had progressed from 0.62 (±0.23) logMAR to 0.82 (±0.29; $P < 0.001$), whereas there was no significant change in BCVA in patients without MH progression ($P = 0.25$). In 31% (16/51) of patients, classification of their MHs (small ≤250 µm, medium 251–400 µm, and large >400 µm) changed over the 4-week period.

**Conclusions:** Using a cutoff discriminates change from measurement error. A significant proportion of MHs progressed by 4 weeks, particularly in the presence of VMT.

**Translational Relevance:** The established cutoff enables clinicians to differentiate true MH enlargement from measurement error.

## Introduction

Macular holes (MHs) are considered an indication for non-urgent, elective vitreoretinal surgery, which leaves an uncertain time frame as to when these patients should undergo surgery. Although pars-plana vitrectomy (PPV) with internal limiting membrane (ILM) peel and gas tamponade is the standard surgical treatment, other treatment options may be considered based on the minimum linear diameter (MLD) and other characteristics, such as the presence of vitreomacular traction (VMT).[1–6]

It is known that the majority of MHs enlarge if untreated, however, the time frame is not clear. Most previous observations have been made over the course of several months to several years based on biomicroscopic examinations, fundus photographs, and fluorescein angiograms, and at a time when optical coherence tomography (OCT) was not available.[7–10]

One recent study demonstrated the enlargement of MHs based on high-density linear OCT scans over a period of 2 to 47 weeks, particularly if associated with VMT.[11] The definition, however, of what constitutes enlargement is not clear. Measurement of the MLD was performed manually by an observer using the OCT software caliper tool. Consequently, determination of the MLD and progression is subject to intra- and inter-observer error. For example, Madi et al.[11] reported a reduction in MH size of between −6 and −82 µm in 7 cases and an enlargement of between 5 and 260 µm in 34 cases, based on one reading by one observer.

Without knowing measurement precision, it is difficult to know what proportion of cases represent an actual change in MH size and what is measurement error.

The aim of this study was, therefore, to determine the precision of MH size measurement using high-density radial OCT scans in order to determine the cutoffs for a change in MH size. These cutoffs were then used to investigate if there was significant short-term enlargement of MH size over a 4-week period.

## Material and Methods

This is a retrospective analysis of consecutive patients who presented with an MH to the Ophthalmology Department, Hospital rechts der Isar, Technical University of Munich, Germany, between July 2018 and January 2021, and who had been on the waiting list for surgery for a period of 4 weeks (range 3 to 5 weeks). Inclusion criteria were the presence of an idiopathic full-thickness MH. Exclusion criteria were secondary MHs, myopia >8 diopters, co-existing ocular pathology apart from cataract, and previous ocular surgery apart from cataract surgery.

Patient data collected included age, sex, duration of the MH based on the duration of symptoms, and lens status (phakic or pseudophakic). Best corrected visual acuity (BCVA) was obtained at first presentation (baseline) and after 4 weeks prior to surgery, using a decimal chart. For statistical analysis, the readings were converted to the logarithm of the minimum angle of resolution (logMAR). Patients underwent a high-density radial OCT scan (48 sections) at initial presentation as well as after 4 weeks before the surgery. The center point of the radial pattern scan was manually centered on the center of the MH, while requesting the patient to focus on a target light presented to the fellow eye. A TruTrack active eye tracking system (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) was used to enable best available concordance between repeat scans of the same MH. All OCT images were evaluated in the 1:1 µm mode by 2 independent observers (vitreoretinal consultants) and the presence or absence of VMT and of an epiretinal membrane (ERM) were noted. Each observer measured the MLD size of the MHs at baseline and after 4 weeks. These measurements were performed 3 times by each observer for the same MH both at baseline and after 4 weeks. The observers were masked to each other´s readings as well as to their previous readings.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Technical University of Munich (TUM) on the February 16, 2021 (Registration Number: 80/21 S). Patient consent was waived due to the retrospective nature of the data analysis (Article 27 Data Protection BayKrG, Bavarian Hospital Law).

### Statistical Analysis

To assess repeatability (intra-observer agreement) and reproducibility (interobserver agreement) Bland-Altman analyses were performed. The primary measurement of each observer was used to calculate the mean for each MH and the difference between the two sets of measurements for each MH plotted against their mean. Measurements were tested for normality (Shapiro-Wilk) and homogeneity of variance (Levene). An analysis of variance (ANOVA) was used to test for proportional bias and to compare means between the sets of measurements within the two repeat sets of measurements of each observer, and between the first and among all three sets of measurements for both observers. Coefficients of repeatability (CR) were calculated as 2SD. Limits of agreement (LOA) with 95% and 99.73% confidence intervals (CIs) were calculated for all mean differences, with the 99.73% LOA using the mean of 3 measurements, which are known to be narrower (more precise) than the 95% LOA using one measurement of each observer.[12]

The cutoffs for MH size change were calculated as the outer confidence limits for the 95% and 99.73% LOA ($CL_{LOA}$) for a normal distribution with $CL_{LOA} = \overline{mean} \pm kSD$ (Equation 10) and $k_{approx} = 1.96 + t_{0.975,\, n-1}\frac{\sqrt{2.92}}{\sqrt{n}}$ (Equation 14) of Carkeet and Goh (for $n > 40$).[13] The value $k$ (tolerance factor) determines that a minimum proportion of 95% (t = 1.96) or 99.73% (t = 3.00) of the population lies between $mean \pm kSD$ for the outer 95% and 99.73% LOA. The 99.73% cutoffs were then used to determine which MH had changed.

Univariate analysis was performed for MH size change with each of the following variables: VMT, ERM, age, sex, duration of symptoms, BCVA, and lens status (phakic or pseudophakic) using a Kruskal Wallis test. All variables that were significantly associated with MH change were included in a generalized binary linear model.

Continuous variables were reported as mean (± standard deviation). Level of significance was set at $P < 0.05$. A Bonferroni correction was made for multiple tests.

## Results

Fifty-one eyes of 51 patients were included (19 men and 32 women) with a mean age of 66.06 years (±9.02 years) and a mean symptom duration of 20.37 weeks (±25.06 weeks). Thirty-nine (76.5%) patients were phakic and 12 (23.5%) were pseudophakic. Mean time interval between the OCT scans at first presentation (baseline) and after 4 weeks was 28.59 days (±7.52 days). An ERM was present in 8 of 51 (15.7%) patients and 17 of 51 (33.3%) patients had an associated VMT, which had released in 2 of 17 (11.76%) eyes after 4 weeks without MH closure.

Mean MLD MH size at baseline was 334 µm (±179 µm; range 39 to 793 µm) and after 4 weeks

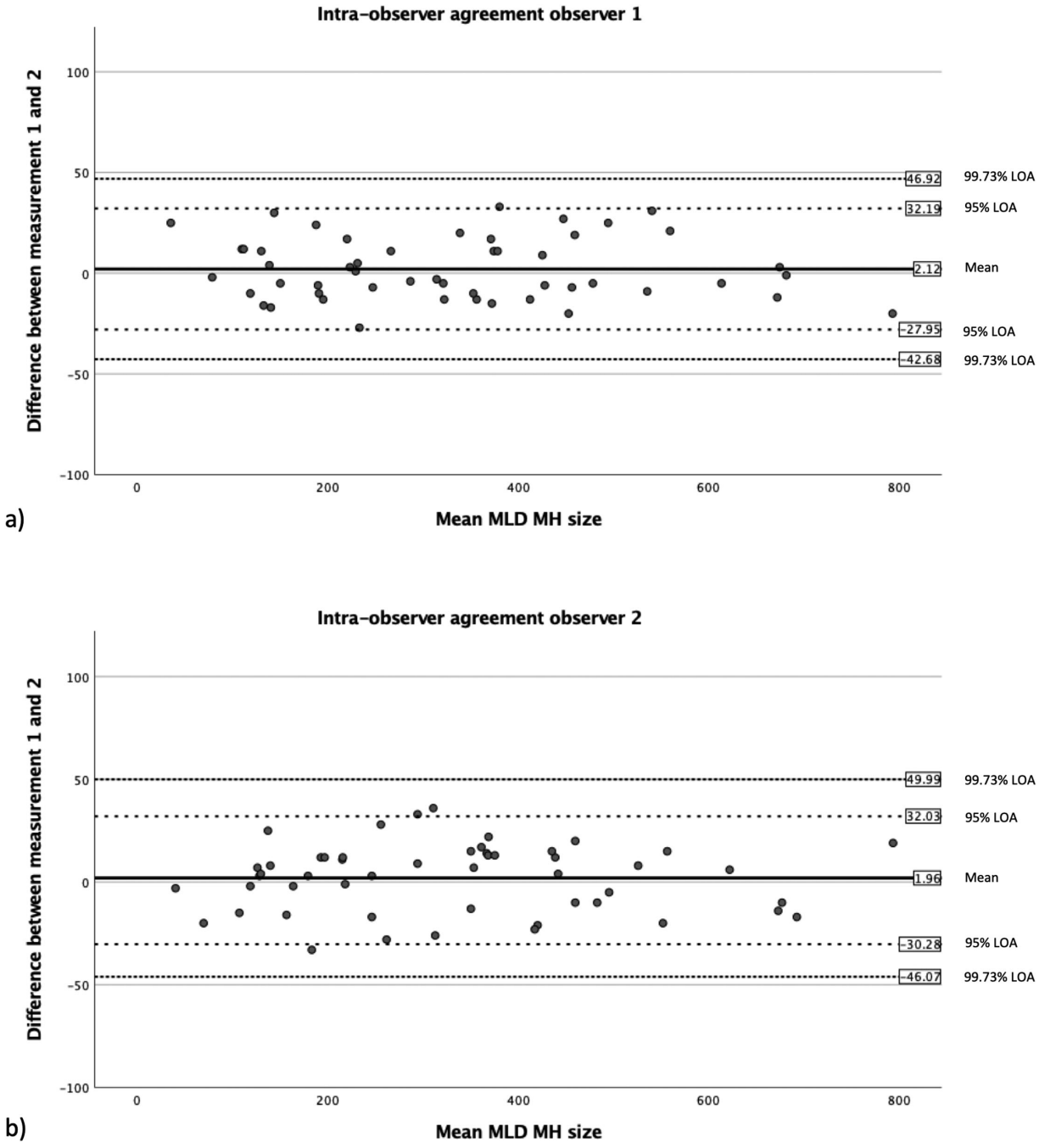


**Figure 1.** Bland Altman Blots for the intra-observer agreements for observer 1 (**a**) and observer 2 (**b**). The differences of the MLD measurements are plotted against their mean.

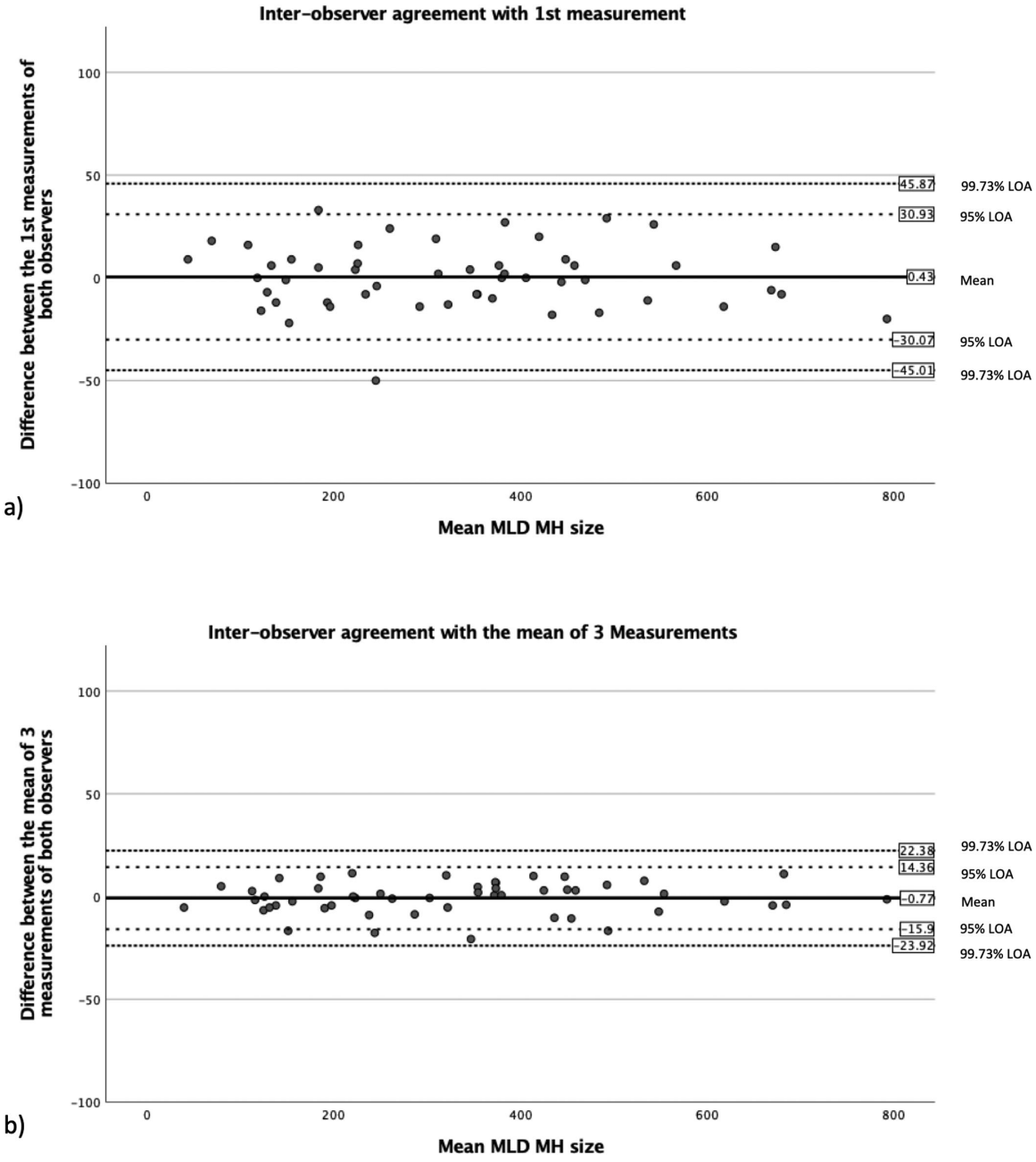


**Figure 2.** Bland Altman Blots for the interobserver agreements between both observers based on one single measurement of each MH by each observer (**a**) and based on the mean of three repeat measurements of each MH by each observer (**b**). The mean of three measurements reduces the variance thus narrowing the limits of agreement (LOA) and improving precision.

392 µm (±166 µm), with a mean difference of 57.39 µm (±68.93 µm; $P < 0.001$). At baseline 21 (41.2%) MHs were ≤250 µm, 13 (25.5%) MHs were 251 to 400 µm, and 17 (33.3%) MHs >400 µm, and, after 4 weeks, 12 (23.5%) MHs were ≤250 µm, 16 (31.4%) MHs were 251 to 400 µm and 23 (45.1%) MHs were >400 µm. Mean BCVA deteriorated by 0.10 (±0.19) logMAR from 0.63 (±0.25) at baseline to 0.73 (±0.28) logMAR after 4 weeks ($P < 0.01$).

The CR for intra-observer agreement (repeatability) between the first and second series of measurements were 31 µm for observer 1 ($P = 0.33$) and 33 µm for observer 2 ($P = 0.40$), and the CR for interobserver agreement (reproducibility) between the two observers first set of measurements was 31 µm ($P = 0.84$), reducing to 15 µm ($P = 0.48$) between the mean of their 3 sets of measurements.

Differences between measurements to their mean together with the 95% and 99.73% LOA are displayed as Bland Altman plots for the first two measurements of each observer (Fig. 1), and for the first measurements of both observers as well as for the mean of three repeat measurements of both observers (Fig. 2). There was homogeneity of variance of the differences in MLD measurements across all MH sizes ($P = 0.58$) and no bias, indicating that the differences in measurements were not related to the magnitude of the MH size.

Using the mean of 3 repeat measurements the confidence limits for the outer 95% and 99.73% LOA ($CL_{LOA}$) for an increase in MLD were 19.68 µm and 30.03 µm, and for a decrease in MLD −18.14 µm and −28.4 µm, respectively.

MHs were therefore classified as having progressed in size if the mean MLD had increased by ≥31 µm in the OCT scans at 4 weeks compared to baseline and reduced in size if the MLD had decreased by ≥29 µm. Using these cutoff values, 23 of 51 (45%) of MHs increased in size over the 4-week period and no MH became smaller.

Increase of MH size in the 4-week period was significantly associated with the presence of VMT ($P < 0.001$), MLD size at baseline ($P = 0.03$), and duration of symptoms ($P = 0.02$), but not with the number of days between OCT scans ($P = 0.92$), sex ($P = 0.14$), age ($P = 0.51$), lens status ($P = 0.79$), or the presence of an ERM ($P = 0.49$). Mean MLD MH size at baseline was larger in MHs that did not progress (387 µm, ±194 µm) than in MHs that progressed (271 µm [±138 µm], $P = 0.02$). MH size increased in 9 of 34 (26.5%) of patients without VMT and in 14 of 17 (82.4%) of patients with VMT ($P < 0.001$), with a mean increase in MH size of 91 µm (±41 µm) and 137 µm (±62 µm), respectively ($P = 0.065$).

Although there was no significant reduction in BCVA during the 4 weeks in patients without MH progression (0.63 [±0.27] to 0.66 [±0.27], $P = 0.25$), BCVA deteriorated in patients in whom the MH had progressed by 0.20 (±0.21) logMAR (0.62 [± 0.23] to 0.82 [±0.29], $P < 0.001$).

There were no differences between patients without or with VMT in terms of number of days between repeat OCT scans from first presentation to 4 weeks (29.3 [±7.9] vs. 27.2 [±6.6] days, $P = 0.23$), age (65.6 [±10.0] vs. 67.0 [±6.7] years, $P = 0.38$), duration of symptoms (19.1 [±17.6] vs. 23.1 [±37.2] weeks, $P = 0.30$), BCVA at baseline (0.63 [±0.24] vs. 0.63 [±0.27] logMAR, $P = 0.65$), and the presence of an ERM ($P = 0.70$). Mean MLD size at baseline, however, was larger in MHs without VMT (370 [±183] µm) than in MHs with VMT (262 [±149] µm, $P = 0.04$) and there were more phakic patients in the group with VMT ($P = 0.04$).

In the generalized linear model, there was a significant association between progression of MHs and the presence of VMT at baseline ($P = 0.008$) but not with MLD size at baseline ($P = 0.84$) or duration of symptoms ($P = 0.13$).

## Discussion

Because MHs have been shown not to be perfectly round in shape[14] and their MLD may lie in any meridian, we routinely use a high-density radial OCT scan pattern, which considers all meridians and is likely to improve detection of the largest MLD as compared to a horizontal linear one. As far as we are aware, cutoffs for deciding if an MH has increased or decreased in size have not previously been determined. We used the mean of three measurements, which has been shown to significantly improve precision of measurement.[12] This is crucial to differentiate between true change in MH size versus measurement error. Using the confidence limits around the upper 99.73% LOA, a 31 µm change in MH size between baseline and 4 weeks was defined as cutoff for increase (and −29 µm for decrease) in MLD size of an MH. This cutoff was independent of the size of the MH. If only 1 measurement of each rater were used, the cutoff would be >60 µm.

The timing of vitreoretinal (VR) surgery is influenced by several factors including the expected impact on anatomical and functional outcomes. For small MHs associated with VMT, some surgeons may even prefer to wait for a few weeks to allow for spontaneous resolution of VMT and MH closure to avoid surgery.[15] Whereas the reported rate of spontaneous resolution of VMT is about 10% to 32%,[16–18] MH closure despite VMT release lies only within 2.7% to 8.6% over the course of several months.[7,15,19,20] Madi et al.[11] observed spontaneous release of VMT in 70% of eyes over a median period of 8 weeks with no case of spontaneous MH closure. In our series, 11.76% of VMT released after 4 weeks without MH closure, whereas 88.2% of MHs with VMT progressed in size and accompanied by a significant drop in BCVA. Our findings support those of Madi et al.[11] for the presence of VMT as the outstanding risk factor for progression. They compared the readings of one observer on high-density horizontal linear OCT scans at baseline and at a median of 8 weeks and noted that the number of large MHs >400 µm had increased from 24% to 49%, whereas we found an increase from 33% to 45% within 4 weeks. This may also be influenced by the different

OCT scan patterns used and the variable duration of symptoms prior to presentation.

Several treatment options for MHs exist depending on their OCT characteristics and the surgeon's and patient's preference, with the treatment strategies usually decided upon at the time the patients are listed for surgery. In patients with MHs ≤400 µm associated with VMT, treatment with ocriplasmin is an option. The success rate, however, reduces from 58% for MHs ≤250 µm to only 25% for MHs 251 to 400 µm,[1] hence some surgeons prefer a primary PPV in MHs >250 µm irrespective of the presence or absence of VMT. For large MHs >400 µm ocriplasmin is no longer an option,[2] some surgeons may even consider using an ILM-flap during PPV to increase the chance of MH closure, which is known to decrease in large MHs.[3–6] We found in our series that in 31% (16/51) of patients the choice of treatment on the day of listing would have potentially changed by the time of the scheduled operation 4 weeks later. In 9 patients, their MHs were no longer ≤250 µm and 6 were then also no longer eligible for ocriplasmin. In addition, seven patients planned for PPV with routine ILM-peeling also received an ILM-flap due to the increase in MH size. Furthermore, the choice of the type of gas tamponade and the duration of advised postoperative face-down posturing also depends on the size of the MH.[21,22] This not only emphasizes the need for a repeat OCT scan just prior to the planned procedure to adjust the surgical approach if required, but also the need for having a defined cutoff for what constitutes a change in MH size.

Our study has several limitations. It includes only moderate numbers with repeat imaging at only two time points. Although the observers were masked, it is possible that the time period between the two sets of OCT images influenced the measurements of the MHs between baseline and 4 weeks. However, the cutoff value was calculated based only on the repeat measurements of the MLD size at baseline, to which both observers were masked. Even though the repeat OCT scans were taken in the TruTrack mode, there will be an error associated with repeat scanning which we did not measure, and which would likely increase the cutoff value for progression. The provision of cutoffs, however, for a change in MH size using radial OCT scans will be helpful for deciding on progression. Additional work is required to measure inter-OCT device precision so that cutoffs for change can be determined and generalized between different centers, and further studies are needed to assess the effect of the size progression on the postoperative visual outcome.

In summary, we have for the first time provided cutoffs for determining MH size progression and applied these cutoff values to patients awaiting MH surgery for a period of 4 weeks. We could demonstrate that MHs progress at a quicker rate than has been apparent particularly in the presence of VMT, accompanied by deterioration in pre-operative BCVA. Because this may impact on the choice of treatment, MHs should be re-evaluated just prior to surgery based on a repeat OCT scan.

## Acknowledgments

Disclosure: **C. Baumann**, None; **S. Hoffmann**, None; **A. Almarzooqi**, None; **N. Johannigmann-Malek**, None; **C.P. Lohmann**, None; **S.B. Kaye**, None

## References

1. Stalmans P, Benz M, Gandorfer A, et al. Enzymatic vitreolysis with ocriplasmin for vitreamacular traction and macular holes; MIVI-TRUST Study Group. *N Engl J Med*. 2012;367(7):606–615.
2. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology*. 2013;120(12):2611–2619.
3. Lois N, Burr J, Norrie J, et al. Internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole: a pragmatic randomized controlled trial. *Invest Ophthalmol Vis Sci*. 2011;52(3):1586–1592.
4. Steel DH, Donachie PHJ, Aylward GW, et al. Factors affecting anatomical and visual outcome after macular hole surgery: findings from a large prospective UK cohort. *Eye (Lond)*. 2021;35(1):316–325.
5. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology*. 2010;117(10):2018–2025.
6. Baumann C, Kaye S, Iannetta D, et al. Effect of inverted internal limiting membrane flap on closure rate, post-operative visual acuity and restoration of outer retinal layers in primary idiopathic macular hole surgery. *Retina*. 2020;40(10):1955–1963.
7. Chew EY, Sperduto RD, Hiller R, et al. Clinical course of macular holes: the Eye Disease Case-Control Study. *Arch Ophthalmol*. 1999;117(2):242–246.
8. Kim JW, Freeman WR, El-Haig W, et al. Baseline characteristics, natural history, and risk factors to progression in eyes with stage 2 macu-

lar holes. Results from a prospective randomised clinical trial. Vitrectomy for Macular Hole Study Group. *Ophthalmology*. 1995;102(12):1818–1829.
9. Hikichi T, Yoshida A, Akiba J, Trempe CL. Natural outcomes of stage 1, 2, 3, and 4 idiopathic macular holes. *Br J Ophthalmol*. 1995;79(6):517–520.
10. Casuso LA, Scott IU, Flynn HW, et al. Long-term follow-up of unoperated macular holes. *Ophthalmology*. 2001;108(6):1150–1155.
11. Madi HA, Dinah C, Rees Rees J, Steel DHW. The Case Mix of Patients Presenting with Full-Thickness Macular Holes and Progression before Surgery: Implications for Optimum Management. *Ophthalmologica*. 2015;233(3-4):216–221.
12. Brunner M, Czanner G, Vinciguerra R, et al. Improving precision for detecting change in the shape of the cornea in patients with keratoconus. *Sci Rep*. 2018;8(1):12345.
13. Carkeet A, Goh YT. Confidence and coverage for Bland-Altman limits of agreement and their approximate confidence intervals. *Stat Methods Med Res*. 2018;27(5):1559–1574.
14. Chen Y, Nasrulloh AV, Wilson I, et al. Macular hole morphology and measurement using an automated three-dimensional image segmentation algorithm. *BMJ Open Ophthalmol*. 2020;5(1):e000404.
15. Privat E, Tadyoni R, Gaucher D, et al. Residual defect in the foveal photoreceptor layer detected by optical coherence tomography in eyes with spontaneously closed macular holes. *Am J Ophthalmol*. 2007;143(5):814–819.
16. Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. *Am J Ophthalmol*. 1995;119(1):55–61.
17. Johnson MW. Posterior vitreous detachment: evolution and complications of its early stages. *Am J Ophthalmol*. 2010;149(3):371–382.
18. Tzu JH, John VJ, Flynn HW, Jr, et al. Clinical course of vitreomacular traction managed initially by observation. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(5):571–576.
19. Freeman WR, Azen SP, Kim JW: Vitrectomy for the treatment of full-thickness stage 3 or 4 macular holes. Results of a multicentred randomised clinical trial. The Vitrectomy for Treatment of Macular Hole Study Group. *Arch Ophthalmol*. 1997;115(1):11–21.
20. Yuzawa M, Watanabe A, Takahashi Y, Matsui M. Observation of idiopathic full-thickness macular holes. Follow-up observation. *Arch Ophthalmol*. 1994;112(8):1051–1056.
21. Yorston D, Siddiqui MAR, Awan MA, et al. Pilot randomised controlled trial of face-down posturing following phacovitrectomy for macular hole. *Eye (Lond)*. 2012;26(2):267–271.
22. Alberti M, la Cour M. Face-down positioning versus non-supine positioning in macular hole surgery. *Br J Ophthalmol*. 2015;99(2):236–239.