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Quantitative Analyses of Retinal Traction Force and Metamorphopsia in Lamellar Macular Hole and Related Diseases

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Purpose: To investigate the involvement of retinal traction in the pathogenesis of lamellar macular hole (LMH) and related diseases based on OCT–based consensus definition.

Design: Retrospective, observational study.

Participants: Seventy-two eyes with LMH, epiretinal membrane foveoschisis (ERM-FS), or macular pseudohole (MPH).

Methods: To quantitatively evaluate the involvement and strength of retinal traction in their pathogenesis, retinal folds were visualized with en face OCT imaging, and the maximum depth of the parafoveal retinal folds (MDRF) was measured. Metamorphopsia was quantified by measuring the minimum visual angle of dotted lines needed to cause it to disappear using M-CHARTS (Inami).

Main Outcome Measures: Maximum depth of retinal folds and M-CHARTS scores.

Results: Of the 72 eyes, 26 were classified as having LMH, 25 as having ERM-FS, and 21 as having MPH. Parafoveal retinal folds were observed in 7 (26.9%) eyes with LMH, 25 (100%) with ERM-FS, and 21 (100%) with MPH. The MDRF (7.5 $\pm$ 17.6 μm) was significantly smaller in LMH than in ERM-FS (86.3 $\pm$ 31.4 μm) and MPH (74.5 $\pm$ 24.6 μm) (both $P < 0.001$), whereas no significant difference in MDRF between MPH and ERM-FS was observed ($P = 0.43$). A significant positive correlation between MDRF and M-CHARTS scores was observed in ERM-FS and MPH ($P = 0.008$ and 0.040, respectively) but not in LMH ($P = 0.073$).

Conclusions: Retinal traction was significantly weaker in the LMH group than in the ERM-FS and MPH groups. The MDRF was significantly associated with the degree of metamorphopsia in the ERM-FS and MPH groups. These results provide insights into the diseases' pathophysiology and treatment strategy. *Ophthalmology Science 2023;3:100305*

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In 2020, a B-scan OCT–based consensus definition of lamellar macular hole (LMH) and related diseases was established by Hubschman et al.[1] The advent of these uniform diagnostic criteria has had an epoch-making impact on retinal practice. It is expected to resolve long-standing problems associated with LMH, namely, the misinterpretation of the pathogenesis of LMH and related diseases and the confusing use of some associated terminologies.

According to the consensus definition by Hubschman et al.,[1] the most important parameter for classifying LMH and related disorders is retinal traction. They used B-scan OCT images to evaluate macular morphology and clearly distinguished LMH, where retinal traction is less involved in its pathogenesis, from epiretinal membrane foveoschisis (ERM-FS) and macular pseudohole (MPH), where retinal traction is involved in their pathogenesis. Consistent with the B-scan imaging findings, investigations using en face imaging also showed that retinal folds caused by retinal traction were observed only in ERM-FS and MPH but not in LMH.[2–5] The evaluation methods used in these studies can qualitatively assess the presence or absence of retinal traction; however, it is challenging to quantitatively assess the traction force on the retina.

Recently, we focused on the depth of retinal folds visualized with en face imaging and observed that this depth is an important objective and quantitative biomarker that reflects the tangential traction force on the retina due to epiretinal membrane (ERM).[2,6–9] We further examined the relationship between the preoperative maximum depth of retinal folds within the parafovea (MDRF) and metamorphopsia. The MDRF is the distance between the 2 planes of en-face OCT images: 1 on the level of the internal limiting membrane (ILM) and the other through the bottom of the deepest retinal fold within the parafoveal area (Figure S1). As a result, we found that MDRF was significantly related to preoperative metamorphopsia in eyes with idiopathic ERM.[10]

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Therefore, the study aimed to quantitatively evaluate retinal traction using en face imaging for LMH and related diseases diagnosed according to the consensus definition and determine its relationship with visual function.

Methods

Study Design and Participants

In this retrospective observational study, we reviewed the medical records of 65 consecutive patients (72 eyes) who were diagnosed with LMH, ERM-FS, or MPH and visited the Okayama University Hospital between October 2016 and July 2021. Patients with high myopia (spherical equivalent ≤ -6 diopters or axial length ≥ 26.0 mm), macular pucker, diabetic maculopathy, age-related macular degeneration, retinal vein occlusion, or active uveitis were excluded. All investigative procedures were conducted in accordance with the tenets of the Declaration of Helsinki, and the study was approved by the ethics committee of the Okayama University Hospital, Okayama, Japan (Reference number: K2205-010). Written informed consent was obtained from all the participants.

Ophthalmic Examinations

All patients underwent comprehensive ophthalmic examinations, including best-corrected visual acuity testing with refraction using a 5-m Landolt C acuity chart and indirect and contact lens slit-lamp biomicroscopy. Metamorphopsia was quantified using M-CHARTS (Inami), a chart with 19 dotted lines with dot intervals of between 0.2° and 2.0° visual angles. The minimum visual angle of the dotted lines needed to cause the metamorphopsia to disappear was measured. The axial length was measured using an optical biometer (OA-2000; Tomey).

Image Acquisition Using Swept-Source OCT

All OCT imaging procedures were performed using a swept-source OCT (DRI OCT-1 Triton; Topcon Corporation). For B-scan imaging, horizontal and vertical scans centered at the fovea were obtained. The obtained B-scan images were analyzed and classified as LMH, ERM-FS, or MPH, according to the

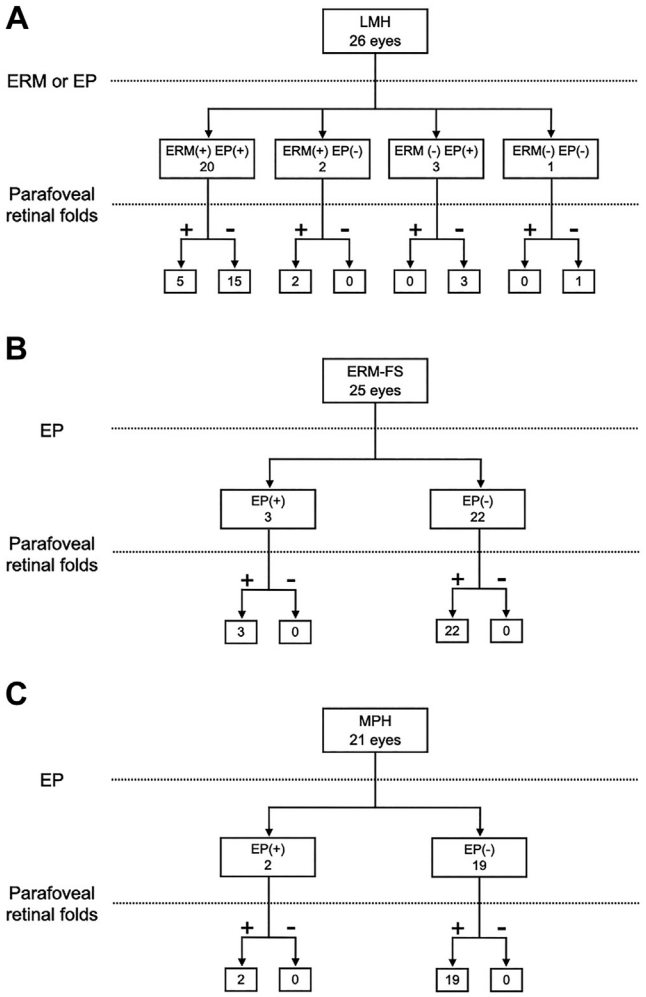

Figure 1. Flow chart classifying lamellar macular hole (LMH) (**A**), epiretinal membrane foveoschisis (ERM-FS) (**B**), and macular pseudohole (MPH) (**C**) based on the presence or absence of abnormal retinal surface findings and parafoveal retinal folds. EP = epiretinal proliferation; ERM = epiretinal membrane.

OCT-based consensus definition proposed in 2020. Briefly, the mandatory criteria for LMH are the presence of (1) irregular foveal contour, (2) foveal cavity with undermined edges, and (3) apparent loss of foveal tissue; those for ERM-FS are the presence of (1) contractile ERM and (2) foveoschisis to the level of Henle's fiber layer; and those for MPH are the presence of (1) foveal center–sparing ERM, (2) retinal thickening, and (3) verticalized or steepened foveal profile. We defined ERM as high-intensity linear lines seen on the retinal surface and epiretinal proliferation (EP) as uniform low-intensity lesions on the retinal surface. For en face imaging, 3-dimensional OCT volume data of the retina were obtained over a 6 × 6-mm area consisting of 512 × 512 A-scans. Image analysis software (IMAGEnet6, Version 1.22 software, Topcon Corporation) was used to construct en face images flattened at the level of the ILM. The ERM was visualized as hyperreflective lesions using en face images at the ILM level. Retinal folds were visualized as hyporeflective linear lesions using en face images below the ILM level. To quantitatively evaluate the strength of retinal traction, the MDRF was measured according to previous reports.[6–10] Briefly, the distance between the ILM surface and the surface on which the deepest retinal folds are seen was measured in the parafoveal area, i.e., a circle 3 mm in diameter centered on the fovea.

Statistical Analysis

Best-corrected visual acuity was measured using a Landolt C chart in decimal units and subsequently converted to the logarithm of the minimal angle of resolution units. Data are presented as mean ± standard deviation. Continuous variables were compared using either Student *t* test or 1-way analysis of variance, followed by a Bonferroni post hoc test. Fisher exact test was used to analyze categorical variables. The Kruskal–Wallis rank sum test and post hoc Steel–Dwass test were used to compare MDRF in LMH, ERM-FS, and MPH. The Spearman rank correlation test was used to analyze the relationships between MDRF and best-corrected visual acuity and MDRF and M-CHARTS scores. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing).

Results

Of the 72 eyes, 26 were classified as having LMH, 25 as having ERM-FS, and 21 as having MPH. No significant differences were observed regarding age, sex, or axial length. Regarding visual function, there was a significant difference in logarithm of the minimal angle of resolution best-corrected visual acuity ($P = 0.016$) but not in the M-CHARTS score ($P = 0.260$). Analysis of abnormal retinal surface findings using B-scan images revealed ERM or EP in 25 eyes (96.2 %) with LMH. In addition, 22 (84.6%) eyes with LMH had ERM and 23 (88.5%) had EP. Both ERM and EP were present in 20 (76.9%) eyes with LMH (Fig 1A). Since ERM-FS and MPH include the presence of ERM as an essential diagnostic criterion, all eyes had ERM. Of these, 3 (12.0%) eyes of ERM-FS and 2 (9.5%) of MPH had concomitant EP (Fig 1B, C, respectively). En face images at deeper levels than the ILM showed parafoveal retinal folds in 7 (26.9%) eyes with LMH, 25 (100%) with ERM-FS, and 21 (100%) with MPH (Fig 1A–C). Significant differences were observed in the rates of ERM ($P = 0.033$), EP ($P < 0.001$), and parafoveal retinal folds ($P < 0.001$). Disruption of the ellipsoid zone was observed in 17 (65.4%) eyes with LMH, none with ERM-FS, and 1 (4.8%) with MPH, with significant differences between diseases ($P < 0.001$). By comparing visual acuity in LMH with and without ellipsoid zone disruption, the former was significantly worse than the latter (0.33 ± 0.31 and 0.08 ± 0.14, respectively; $P = 0.036$). A summary of the results is presented in Table 1. Typical B-scan and en face OCT images for each group are shown in Figure 2.

Subsequently, we measured MDRF to quantitatively investigate the strength of retinal traction in each disease. The results showed that MDRF was 7.5 ± 17.6 in LMH, 86.3 ± 31.4 in ERM-FS, and 74.5 ± 24.6 μm in MPH, with significant differences between LMH and ERM-FS, and between LMH and MPH; however, the difference between ERM-FS and MPH was not significant (LMH vs. ERM-FS,

Table 1. Clinical Characteristics and OCT Findings of Patients With LMH, ERM-FS, and MPH

	LMH (n = 26)	ERM-FS (n = 25)	MPH (n = 21)	*P* Value
Age (years)	73.1 ± 9.5	69.4 ± 8.4	71.5 ± 7.3	0.318*
Sex (female/male)	16/10	16/9	11/10	0.722†
BCVA (logMAR)	0.24 ± 0.28	0.08 ± 0.13	0.12 ± 0.14	0.016*,‡
M-CHARTS score	0.57 ± 0.61	0.29 ± 0.38	0.41 ± 0.45	0.260*
Axial length (mm)	23.8 ± 1.3	24.0 ± 0.9	23.4 ± 1.3	0.363*
ERM (eyes)	22 (84.6%)	25 (100%)	21 (100%)	0.033†,‡
EP (eyes)	23 (88.5%)	3 (12.0%)	2 (9.5%)	< 0.001†,‡
Parafoveal retinal folds (eyes)	7 (26.9%)	25 (100%)	21 (100%)	< 0.001†,‡
EZ disruption (eyes)	17 (65.4%)	0 (0%)	1 (4.8%)	< 0.001†,‡

BCVA = best-corrected visual acuity; EP = epiretinal proliferation; ERM = epiretinal membrane; ERM-FS = epiretinal membrane foveoschisis; EZ = ellipsoid zone; LMH = lamellar macular hole; logMAR = logarithm of the minimal angle of resolution; MPH = macular pseudohole.
*One-way analysis of variance.
†Fisher exact test.
‡$P < 0.05$.

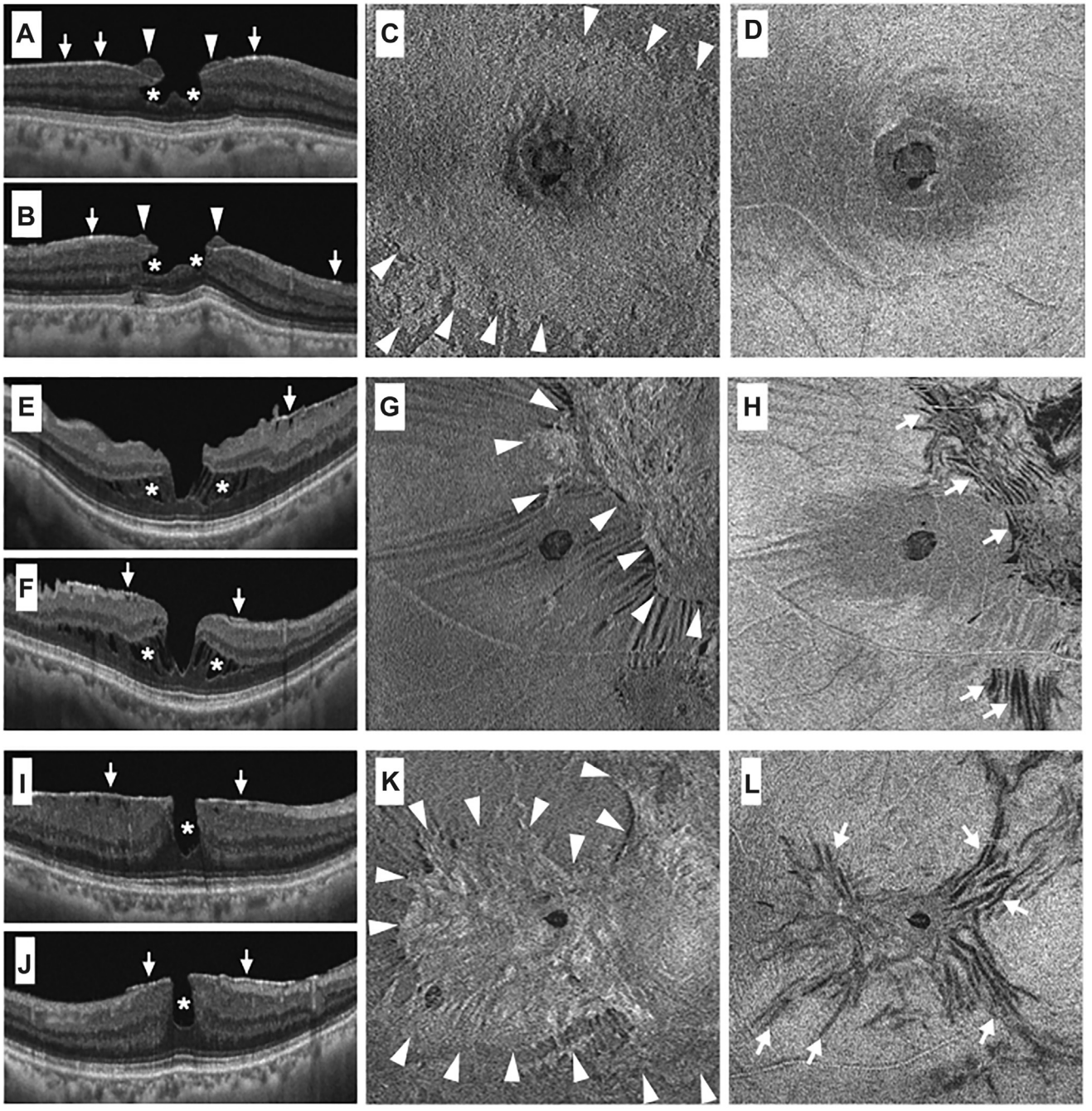

Figure 2. Representative B-scan and en face OCT images of lamellar macular hole (LMH), epiretinal membrane foveoschisis (ERM-FS), and macular pseudohole (MPH). The left column shows the horizontal (**A, E, I**) and vertical (**B, F, J**) B-scan images. The middle and right columns show en face images obtained at the internal limiting membrane (ILM) level and 30 μm below the ILM level. **A—D,** A woman in her 80s with LMH. B-scan images showed epiretinal membrane (ERM) (arrows in **A** and **B**) and epiretinal proliferation (arrowheads in **A** and **B**), a uniform low-intensity lesion on the retinal surface. The foveal contours are irregular with undermined edges (asterisks in **A** and **B**). En face images showed a hyperreflective membrane-like lesion in the superficial retina (arrowheads in **C**) and no retinal folds in the deeper layers. **E—H,** A man in his 60s with ERM-FS. B-scan images showed ERM with retinal folds (arrows in **E** and **F**) and retinoschisis at the level of Henle's fiber layer (asterisks in **E** and **F**). En face OCT images showed ERM with heterogeneous traction around the fovea in the superficial retina (arrowheads in **G**) and prominent retinal folds in the deeper layers (arrows in **H**). **I—L,** A woman in her 80s with MPH. B-scan images showed ERM with retinal folds (arrows in **I** and **J**) and a verticalized foveal profile (asterisks in **I** and **J**). En face OCT images showed ERM existing around the fovea (arrowheads in **K**) and "bow-tie" shaped retinal folds extending radially from the parafovea (arrows in **L**).

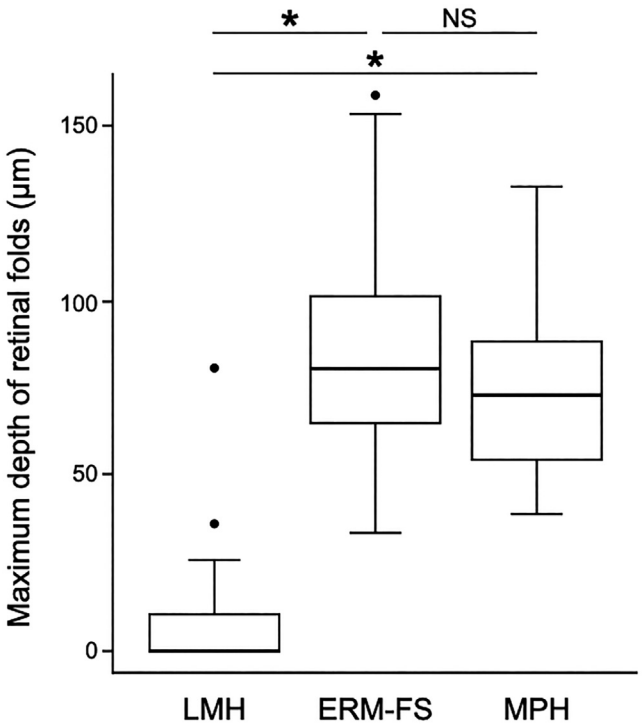

Figure 3. Comparison of maximum depth of retinal folds between lamellar macular hole (LMH), epiretinal membrane foveoschisis (ERM-FS), and macular pseudohole (MPH). The box plot shows the distribution of the maximum depth of retinal folds in each group. Black dots represent outliers. *$P < 0.01$; NS = not significant; Kruskal–Wallis rank sum test and post hoc Steel–Dwass test.

$P < 0.001$; LMH vs. MPH, $P < 0.001$; ERM-FS vs. MPH, $P = 0.43$; Fig 3).

In addition, we examined the association of visual acuity and metamorphopsia with MDRF for each disease. For LMH, neither visual acuity ($P = 0.279$; Fig 4A) nor the M-CHARTS score ($P = 0.073$; Fig 4B) correlated significantly with MDRF. For ERM-FS and MPH, visual acuity was not correlated with MDRF ($P = 0.671$ and $P = 0.898$, respectively; Fig 4C, E); however, the M-CHARTS score correlated significantly with MDRF ($P = 0.008$ and $P = 0.040$, respectively; Fig 4D, F).

Discussion

This study provides the first quantitative evaluation of the strength of retinal traction for 3 diseases classified according to the OCT-based consensus definition.[1] Strong retinal traction was present in the ERM-FS and MPH groups, whereas the retinal traction in the LMH group was very weak, showing a statistically significant difference (Fig 3). Furthermore, a positive correlation was found between MDRF, i.e., the strength of retinal traction, and metamorphopsia in all diseases; however, only ERM-FS and MPH showed a statistically significant correlation. Only 7 of 26 eyes had retinal traction in LMH, and only 1 eye had an MDRF > 69 μm, which Kanzaki et al. proposed as an indication for idiopathic ERM surgery. Therefore, the visual function may be impaired in a traction force-dependent manner in ERM-FS and MPH. Regarding LMH, further study is needed to examine many cases with retinal traction. In contrast, no significant correlation with MDRF was observed for visual acuity in any of the diseases (Fig 4). This is consistent with a previous study by Hirano et al.,[10] who reported a significant correlation between MDRF and metamorphopsia but no significant correlation between MDRF and visual acuity in idiopathic ERM. Therefore, surgical removal of ERM is a suitable treatment for ERM-FS and MPH, while surgical removal of ERM for LMH requires further investigation. This result is consistent with studies that showed that ERM removal is ineffective in LMH[11] and that therapies utilizing EP as a surgical treatment for LMH are useful.[12–14] Therefore, the quantitative assessment of retinal traction by en face imaging is essential for planning treatment strategies in LMH and related diseases.

Lamellar macular hole was first described as a macular morphology formed by the disappearance of the inner wall of cystoid macular edema.[15] Subsequently, histological studies using atypical ERM,[5] whose terminology was unified in the consensus definition as EP, and clinical studies using OCT[2,16] have revealed that retinal traction is not involved in the pathogenesis of LMH. Based on these findings, a consensus definition was proposed by Hubschman et al.[1] in 2020. Despite the fact that there is a consensus that retinal traction is not involved in the pathogenesis of LMH, parafoveal retinal folds were observed in 26.9% of the patients with LMH in this study, suggesting the presence of retinal traction, albeit weaker than ERM-FS and MPH. The reasons for this may be as

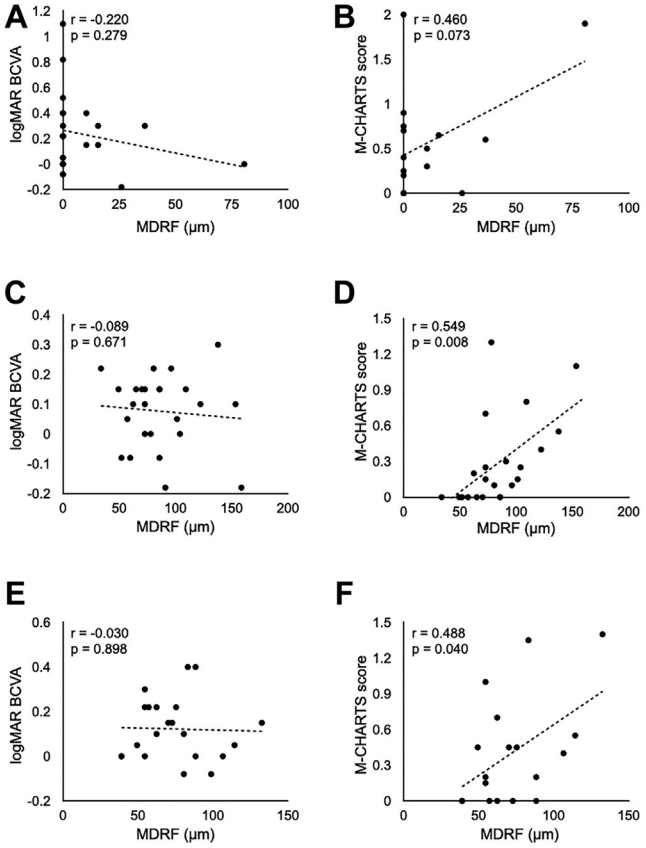

Figure 4. Scatterplots of maximum depth of retinal folds (MDRF) and best-corrected visual acuity (BCVA) in the logarithm of minimal angle of resolution (logMAR) (**A, C, E**) or M-CHARTS scores (**B, D, F**) in lamellar macular hole (**A, B**), epiretinal membrane foveoschisis (**C, D**), and macular pseudohole (**E, F**). Dotted lines represent a regression line.

follows: first, a detailed evaluation of the whole macular region using en face OCT images made it possible to reveal retinal folds that could not be detected by B-scan images. Second, as Hubschman et al. noted, there may be "mixed" lesions with the characteristics of each disease. Third, there may be a transition from 1 disease type to another, such as ERM-FS gradually evolving into LMH.[17] Therefore, even in diseases classified by the consensus definition, the involvement of retinal traction in each case may differ. Consequently, when evaluating the pathophysiology of LMH and considering the indication for surgery, it is necessary to evaluate the distribution and degree of retinal traction in the whole macular region using en face OCT images in conjunction with B-scan images.

The primary pathogenesis of ERM-FS and MPH is considered to be retinal traction due to ERM; however, no difference in traction strength between the 2 diseases was observed in this study (Fig 3). Therefore, factors other than retinal traction force, such as localization of the ERM, the direction of retinal traction, and vitreous traction, may have resulted in foveoschisis or a steepened foveal profile. This was, however, not verified in this study. Therefore, further investigation is needed to determine the type of retinal traction that produces differences in the central foveal morphology. The MDRF correlated with distorted vision in both ERM-FS and MPH. It has been reported that the early manifestation of idiopathic ERM is metamorphopsia rather than visual acuity and that metamorphopsia has a significant impact on the patient's quality of life.[18,19] Recently, attempts have been made to determine the surgical indication for idiopathic ERM using MDRF as an objective quantitative parameter to evaluate metamorphopsia,[9] and similar surgical indication criteria should be established for ERM-FS and MPH.

Epiretinal proliferation was also observed in 88.5% of LMH, 12.0% of ERM-FS, and 9.5% of MPH cases and was significantly higher in LMH. Epiretinal proliferation was higher in LMH; however, the MDRF of LMH was low, suggesting that EP is not related to retinal traction, as reported in previous studies.[2,5,20] Our results showed the presence of EP in ERM-FS and MPH, which is consistent with Itoh et al.'s[21] study that EP is not LMH-specific, although it is frequently associated with LMH.

Our study had several limitations. First, it was a retrospective study. Second, the sample size was small. Third, 7 of 65 patients had bilateral diseases; therefore, statistical modeling may have a covariance problem. In addition, although high myopia was excluded, further studies are needed since high myopia is thought to play a significant role, especially in the pathogenesis of LMH.

In summary, we quantitatively evaluated the frequency and strength of retinal traction in 3 diseases using en face

OCT images and classified them using the OCT-based consensus definition, namely, LMH, ERM-FS, and MPH. Retinal traction in the LMH group was significantly weaker than that in the ERM-FS and MPH groups. Additionally, there was a significant association between MDRF and metamorphopsia in the ERM-FS and MPH groups. These results are important for accurately understanding the pathophysiology of each disease and selecting a reasonable treatment strategy.

Footnotes and Disclosures

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Author Contributions:

Conception and design: Mino, Matoba, Morizane

Data collection: Mino, Matoba, Kanzaki, Shiode, Morita

Analysis and interpretation: Mino, Matoba, Kimura, Hosokawa, Morizane

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Overall responsibility: Mino, Matoba, Kanzaki, Shiode, Morita, Morizane

Abbreviations and Acronyms:
EP = epiretinal proliferation; **ERM** = epiretinal membrane; **ERM-FS** = epiretinal membrane foveoschisis; **ILM** = internal limiting membrane; **LMH** = lamellar macular hole; **MDRF** = maximum depth of retinal folds; **MPH** = macular pseudohole.

Keywords:
Epiretinal membrane foveoschisis, Lamellar macular hole, Macular pseudohole, Metamorphopsia, Optical coherence tomography.

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