

Morphological alterations of macular region in fellow eyes of patients with idiopathic full-thickness macular holes detected by optical coherence tomography

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Received: 2024-02-25 Accepted: 2024-08-20

Abstract

• **AIM:** To describe the optical coherence tomography (OCT) features in the fellow eyes of individuals with full-thickness macular holes (FTMHs).

• **METHODS:** This multicenter retrospective study included observational and validation groups, incorporating fellow eyes of patients diagnosed with idiopathic FTMH. OCT images were categorized according to International Vitreomacular Traction Study (IVTS) and Gass classification. Age- and sex-related cataract patients were served as control groups. Vertical and horizontal OCT images were chosen for further measurement. OCT parameters including foveal floor width (FFW), central foveal thickness (CFT) and FFW/CFT ratio were assessed and compared between observational and control groups and were validated by validation group. Receiver operating characteristic (ROC) curves were plotted for OCT parameters in identifying macular holes (MHs).

• **RESULTS:** A total of 73 patients were included in the observational group, comprising 51 females and 22 males, with an average age of 65.5±7.3y and an axial length of 23.9±0.8 mm. The validated group consisted of 47 patients,

including 31 females and 16 males, with an average age of 65.0±7.4y and an average axial length of 23.6±0.8 mm. In the observational group, 16.4% of the fellow eyes associated with FTMHs also exhibited MHs, while in the validated group, this prevalence was 12.7%. The 45.2% in the observational group and 44.6% in validated group of these fellow eyes displayed abnormalities including vitreomacular adhesion (VMA), vitreomacular traction (VMT), and MHs. Statistically significant differences were observed in FFW, CFT, and FFW/CFT ratio between control and observational group, as well as validated group ($P<0.01$), no matter in the vertical or horizontal layer. ROC curves revealed the area under the curve (AUC) for FFW and the FFW/CFT ratio was 0.85 and 0.90, respectively.

• **CONCLUSION:** In the case of unilateral idiopathic MHs, it was important to carefully monitor the condition of the fellow eye. The FFW and FFW/CFT ratio may be good metrics for predicting MHs.

• **KEYWORDS:** optical coherence tomography; macular hole; fovea; foveal floor width; central foveal thickness

DOI:10.18240/ijo.2025.04.10

Citation: Li YT, Chen XZ, Lu YF, Liu YQ, Wu TH, Song ZY, Xie ZG, Lu PR. Morphological alterations of macular region in fellow eyes of patients with idiopathic full-thickness macular holes detected by optical coherence tomography. *Int J Ophthalmol* 2025;18(4):642-647

INTRODUCTION

Idiopathic full-thickness macular hole (FTMH) is a condition affecting the center of the macula, characterized by the complete absence of the retinal neuroepithelial layer. It is more common in older individuals, with a male-to-female ratio of around 1:3^[1]. The annual incidence of primary FTMHs is approximately 7.8–8.7 per 100 000 population^[1-2]. This condition can cause distorted vision and central scotoma, leading to a significantly reduction in visual function.

Optical coherence tomography (OCT) is a widely used method to study retinal and vitreous diseases. It provides detailed

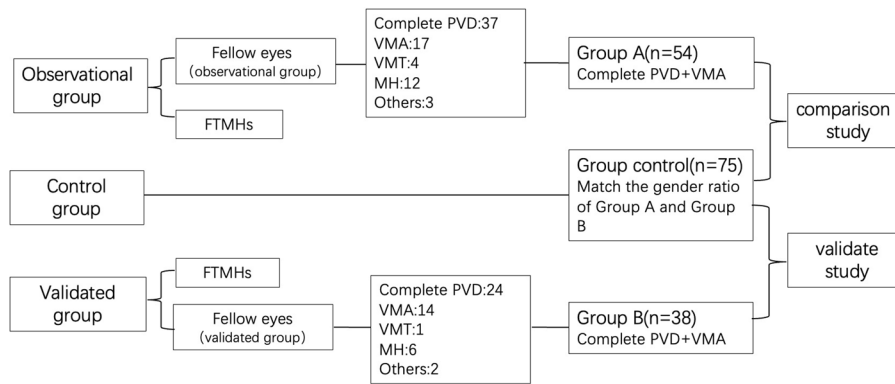


Figure 1 The flowchart of patient selection VMA: Vitreomacular adhesion; VMT: Vitreomacular traction; MH: Macular hole; FTMH: Full-thickness macular hole; PVD: Posterior vitreous detachment.

insights into the retina, including macular holes (MHs). Previous studies have shown that individuals with FTMHs in one eye have a higher risk of developing the same condition in the other eye and the estimated incidence of bilateral MHs ranges from 7.0% to 16.7%^[3-4]. Therefore, it is essential to observe and analyze the macular morphological features in the fellow eyes to identify characteristics with a considerable risk of developing MHs. This can facilitate prompt treatment intervention and reduce the occurrence of MHs.

In the present study, we employed OCT to investigate the morphological features of macular region in fellow eyes of patients with FTMHs, and to determine the risk of developing MHs which may facilitate the early management.

PARTICIPANTS AND METHODS

Ethical Approval This multicenter clinical study was conducted retrospectively at three renowned hospitals namely, the First Affiliated Hospital of Soochow University, Suzhou Eye Ear Nose Throat Hospital, and Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. The research was approved by the Institutional Review Boards (No.2023-492) and was conducted in accordance with the ethical principles outlined in the Helsinki Declaration. The informed consent was obtained.

Methods Individuals diagnosed with idiopathic FTMH and underwent pars plana vitrectomy (PPV) between January 2021 and December 2023 at the First Affiliated Hospital of Soochow University were collected, and the fellow eyes of these patients were enrolled in the observational group. The validated group included the fellow eyes of patients who were diagnosed with idiopathic FTMH and treated by surgeries of PPV between January 2022 and December 2023 at Suzhou Eye Ear Nose Throat Hospital and Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. The patients diagnosed with age-related cataracts between January 2022 and December 2023 at Suzhou Eye Ear Nose Throat Hospital were eligible for inclusion of control group.

The medical records encompassed a thorough medical

history, age, gender, chronic systemic diseases, detailed ophthalmological examinations, and fundus examinations, including axial lengths, visual acuities, and intraocular pressure. Microstructural imaging analysis of the macular fovea in both eyes was conducted using OCT (Heidelberg Engineering, Heidelberg, Germany, or Optovue Inc, Fremont, CA, USA).

Exclusion criteria for the two groups were as follows: 1) age below 50 and above 70 years old, 2) a history of diabetes, systemic diseases, or major systemic illnesses, 3) a history of eye surgeries other than cataract surgery, 4) axial length greater than 26 mm or myopic exceeding 6 D, 5) blurred OCT images. The flowchart of patient selection was presented in Figure 1. Comprehensive ophthalmic examinations of the two groups were collected to provide assessment data. Based on that, two experienced vitreous and retinal specialists, diagnosed and categorize into complete posterior vitreous detachment (PVD), vitreomacular adhesion (VMA), vitreomacular traction (VMT) and MH according to the International Vitreomacular Traction Study (IVTS) consensus-based classification system^[5]. The ones with macular degeneration, epiretinal membrane (ERM) and other retinal diseases were classified to others. In case of differing opinions, an ophthalmology professor, provided further confirmation.

Patients with complete PVD and only VMA, of whom the OCT images showed no observable macular fovea distortion, were separately categorized into Groups A and B for additional measurements and for further comparison study with control group.

As for control group, the patients diagnosed with age-related cataracts between January 2022 and December 2023 at Suzhou Eye Ear Nose Throat Hospital were eligible for inclusion. Exclusion criteria was the same the observational group and validated group. In addition, OCT images with severe macular diseases including vein occlusion, diabetic retinopathy and others resulting in a twisty morphology were excluded. The control group was formed by randomly selecting from cataract

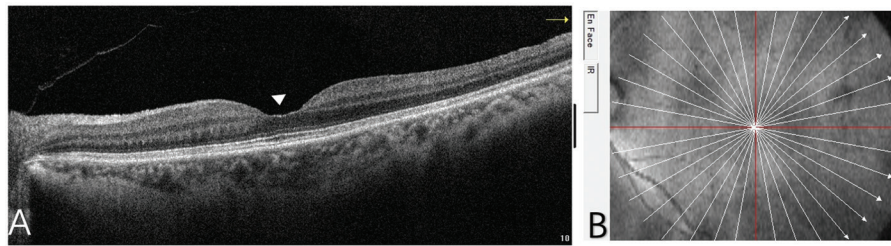


Figure 2 The method of measuring FFW A: Horizontal scan of OCT image with fovea floor width FFW of 529 μm ; B: Enface image in OCT and choose vertical and horizontal scan image. OCT: Optical coherence tomography; FFW: Foveal floor width.

patients to match the age range and gender ratio to facilitate a comprehensive and meaningful comparative analysis.

OCT Measurement OCT examinations were conducted using the radial mode or cross-line mode to make sure to acquire both the horizontal and vertical scan images on eyes with MHs. The OCT machine was carefully positioned as close to the center of the macula as possible. The images with the largest diameters of MHs were chosen for analysis. The built-in measurement tools of the OCT machine were used to measure the parameters of MHs, including the minimum linear diameter (MLD) and base diameter (BD). Two doctors oversaw the measurement process, which was repeated three times to obtain average values.

For fellow eyes of MHs in group A and B, and the eyes in control group, parameters including foveal floor width (FFW) and central foveal thickness (CFT) were measured in both the horizontal and vertical scan images (Figure 2). FFW was defined as the widest distance between the two points where the outer nuclear layer/Henle’s fibre layer reached the inner retinal surface on the OCT slice with the widest floor dimension^[6]. Two experienced doctors used the built-in measuring tool to measure these parameters, repeating the process three times for an average.

Statistical Analysis The data were analyzed using SPSS software [version 28.0.1.0 (142), SPSS Inc., Chicago, IL, USA]. Statistical comparison of parameter including FFW, CFT, and the FFW/CFT ratio between the comparison groups and subgroups were conducted after verifying the distribution, while categorical variables such as gender were analyzed using the Chi-square test. A *P*-value <0.05 was considered statistically significant. A receiver operating characteristic (ROC) curve was plotted using the average of vertical and horizontal data of FFW, CFT and the ratio to predict whether the fellow eye has MH, and the area under the curve (AUC) was calculated.

RESULTS

The observational group included 73 eyes from patients diagnosed with idiopathic MHs. A total of 73 patients were included in the observational group, comprising 51 females and 22 males, with an average age of 65.5 \pm 7.3y and an axial length of 23.9 \pm 0.8 mm. Based on the Gass classification, 36

Table 1 The characteristics of macular eyes in observational group and validated group

Parameters	Observational group	Validated group	<i>P</i>
<i>n</i>	73	47	
Age (y, mean \pm SD)	65.5 \pm 7.3	65.0 \pm 7.4	0.62
AL (mm, mean \pm SD)	23.9 \pm 0.8	23.6 \pm 0.8	0.07
Gender (female/male)	51/22	31/16	0.65
Gass classification (2/3/4)	7/36/30	7/20/20	0.61
MLD (μm , mean \pm SD)	489.5 \pm 176.4	517.5 \pm 231.7	0.32
BD (μm , mean \pm SD)	935.6 \pm 289.7	922.4 \pm 212.6	0.76

AL: Axial length; MLD: Minimal linear diameter; BD: Base diameter.

eyes had stage 3 holes, 30 eyes had stage 4 holes, and 7 eyes had stage 2 holes. The average MLD of the 73 MHs was 489.5 \pm 176.4 μm , and the average BD was 935.6 \pm 289.7 μm . By the same way, the validated group consisted of 47 patients, including 31 females and 16 males, with an average age of 65.0 \pm 7.4y and an average axial length of 23.6 \pm 0.8 mm. In this group, 20 eyes had stage 3 holes, 20 eyes had stage 4 holes, and 7 eyes had stage 2 holes according to Gass classification and the MLD 517.5 \pm 231.7 μm and BD was 922.4 \pm 212.6 μm (Table 1).

After careful examination of OCT images and comprehensive fundus tests on the fellow eyes of FTMHs, in the observational group, there were 3 eyes displayed macular diseases such as macular degeneration and ERM, 37 eyes showed complete PVD, while the remaining 33 eyes were categorized according to the IVTS consensus: 17 eyes (23.3%) were in the VMA phase, 4 eyes were in the VMT stage, and 12 eyes (16.4%) had FTMHs of varying diameters, with or without concomitant VMT. As for the validated group, the results revealed 24 eyes with complete PVD, 14 eyes in the VMA phase, one with VMT, and 6 eyes (12.7%) exhibiting FTMH in the fellow eyes of FTMHs. The 45.2% in the observational group and 44.6% in validated group of these fellow eyes displayed abnormalities including VMA, VMT, and MHs (Table 2).

The patients in the complete PVD and VMA stage, which showing no macular distortion in OCT images, designated as Group to do the comparison study with control one. Group A comprised 54 patients from the observational cohort with

Table 2 The characteristics of fellow eyes in observational and validated group

Parameters	Observational group	Validated group
Compete PVD, <i>n</i> (%)	37 (50.7)	24 (51.1)
Gender (female/male)	26/11	15/9
VMA, <i>n</i> (%)	17 (23.3)	14 (29.8)
Gender (female/male)	10/7	10/4
VMT, <i>n</i> (%)	4 (5.5)	1 (2.1)
FTMH, <i>n</i> (%)	12 (16.4)	6 (12.7)
Small MH with VMT, <i>n</i>	4	1
Larger MH with VMT, <i>n</i>	5	3
MH without VMT, <i>n</i>	3	2
Macular disease, <i>n</i> (%)	3 (4.1)	2 (4.3)

VMA: Vitreomacular adhesion; VMT: Vitreomacular traction; MH: Macular hole; FTMH: Full-thickness macular hole; PVD: Posterior vitreous detachment.

complete PVD and VMA phase, while Group B consisted of 38 patients from the validated cohort. Furthermore, the male-to-female ratio was approximately 1:2, showing a close resemblance between Group A (18 males to 36 females) and Group B (13 males to 25 females).

In the control group, age and sex-matched cataract patients were randomly selected according to exclusion criteria, and a control group of 25 male and 50 female patients was established. Morphological comparisons between Group A, Group B and control group were conducted using parameters of FFW, CFT, and the FFW/CFT ratio. Given the uneven gender distribution, subgroup analysis was also performed to facilitate a more nuanced comparison.

Table 3 showed the values of FFW, CFT, and the FFW/CFT ratio in the horizontal and vertical direction in observational and validated studies. In the two studies, the differences of FFW, CFT, and their ratio between were statistically significant ($P < 0.001$) in the two directional scans.

Average the horizontal and vertical data of FFW, CFT and the FFW/CFT ratio, analyzing these parameters for total and separately for males and females, significant differences were observed between the control group and Group A, as well as control group and Group B (Figure 3). ROC curves were generated. AUC of FFW and the FFW/CFT ratio showed was 0.85 and 0.90, respectively and it may be a predictive factor for FTMH (Figure 4).

Additionally, a special OCT sign of hyperreflective stress lines, which also named of foveal crack lines in OCT images (Figure 5), exhibited a considerable proportion (8 in 14) among patients with a higher value of the ratio exceeding the average. Meanwhile, all these eyes had experienced complete PVD in the macular zone and the majority (12 out of 14) occurred in larger MHs with the diameter larger than 550 μm .

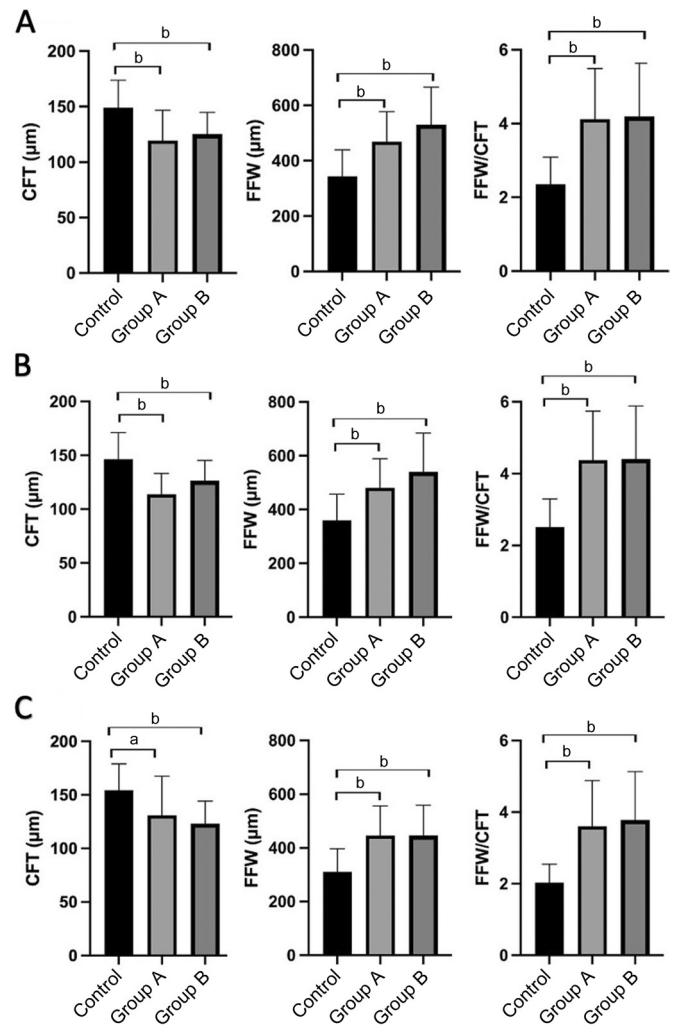


Figure 3 The difference analysis of the comparison and validate study A: Analysis of total which consisted of male and female; B: Analysis of female; C: Analysis of male. ^a $P < 0.05$ and ^b $P < 0.01$. FFW: Fovea floor width; CFT: Central fovea thickness.

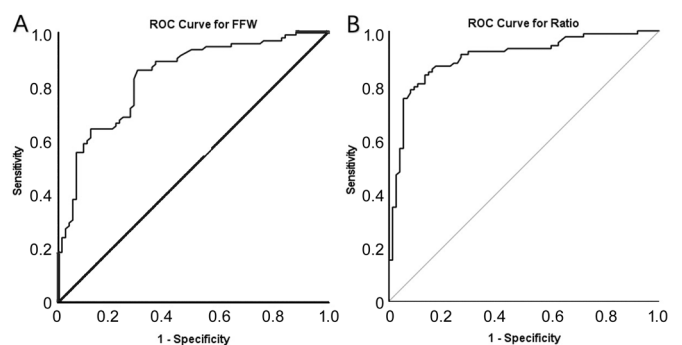


Figure 4 ROC curves of FFW and FFW/CFT ratio and AUC of FFW and the ratio separately was 0.85 and 0.90 FFW: Fovea floor width; CFT: Central fovea thickness; ROC: Receiver operating characteristic; AUC: Area under the curve.

DISCUSSION

Our study provided a comprehensive description of macular morphological abnormalities in the fellow eye of MH, which may predispose individuals to development of MHs. It may consist that eyes tend to be highly symmetrical in retinal and foveal morphology^[7]. Accumulating evidences suggested that

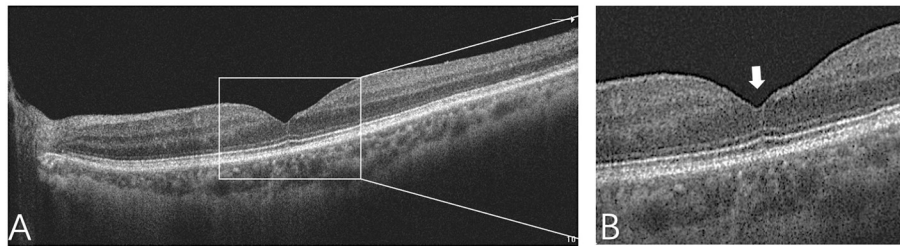


Figure 5 Image of the sign with hyperreflective stress line A: OCT images with hyperreflective stress line; B: The magnification of macular pit in the OCT image. OCT: Optical coherence tomography.

Table 3 Difference of FFW, CFT, and FFW/CFT in two studies

Parameters	Control Mean±SD	Group A		Group B	
		Mean±SD	P	Mean±SD	P
n	75	54		38	
Age (y)	66.6±7.6	64.2±6.3	0.20	64.3±7.5	0.06
Gender (F/M)	50/25	36/18	>0.99	25/13	0.92
AL (mm)	23.90±0.7	23.96±0.7	0.06	23.63±0.8	0.81
Horizontal					
FFW (μm)	345.1±93.8	468.9±108.9	<0.01	508.2±140.0	<0.01
CFT (μm)	149.0±24.8	119.5±27.3	<0.01	125.2±19.4	<0.01
FFW/CFT	2.4±0.7	4.1±1.4	<0.01	4.2±1.5	<0.01
Vertical					
FFW (μm)	364.6±84.8	466.2±105.4	<0.01	514.8±142.0	<0.01
CFT (μm)	155.6±24.6	123.9±25.2	<0.01	129.4±19.9	<0.01
FFW/CFT	2.3±0.4	3.9±1.2	<0.01	4.1±1.4	<0.01

AL: Axial length; FFW: Fovea floor width; CFT: Central fovea thickness.

unilateral MHs may develop into bilateral MHs^[3-4] and there were more than 10% of eyes exhibiting bilateral MHs in our study.

According to IVTS classification, in our study, the proportion of patients with VMA, whether in the observation group (17/73, 23.3%) or the validated group (12/47, 29.8%), was significantly higher than average level and VMA may relieve spontaneously or develop to VMT^[8]. It was plausible that individuals with unilateral MHs may display an abnormal VMA in the fellow eyes compared to normal ones^[4,9-10], when observable changes occurred in the structure of the posterior vitreous, progressing from VMA to VMT^[4]. As for VMT, it was characterized by the anatomical distortion of the fovea, accompanied by perifoveal PVD^[5]. VMT happened earlier than stage 1 MHs and may progress to an advanced stage as FTMH^[11]. Also, VMA and VMT were nearly equal to the stage 0 and stage 1 of Gass classification^[5]. Combined with FTMHs, 45.2% in the observational group and 44.6% in validated group of these fellow eyes displayed different stages of MHs according to Gass classification, which may deteriorate to next stage.

For subjects with undistorted and diseases-free macular fovea, the FFW and CFT parameters were measured, and the ratio of FFW to CFT was calculated in both vertical and horizontal scan images. Compared to the control group, OCT

images in fellow eyes of FTMHs exhibited a noticeable trend characterized by increased width and reduced height in the feature of macular fovea.

It had been proposed that individuals with a wide-based foveal pit may exhibit a predisposition to ERM and MH in their fellow eyes^[12]. Subsequently, through a matched comparison study, their team validated this association in patients with ERM^[13]. In our study, a comprehensive comparative analysis was conducted, revealing distinct patterns in the fellow eyes of FTMHs, which was consistent with this result reported before^[14].

It was hypothesized that it may be linked to embryonic development, as the central Müller cell cone plays a stabilizing role against tangential stress on the central fovea. During ocular growth, intraocular pressure and retinal stretching led to foveal avascular zone more prone to widening than the vascularized retina^[15]. Under certain conditions such as vitreoretinal traction or other forms, these cells may have exhibit weak binding to photoreceptors, rendering them more prone to instability^[4]. Overtimes, MH developed.

When analyzing within gender, it was reported males tend to have a thicker retinal layer than females, and females tend to have a shallower and broader foveal pit^[16]. It was suggested that centrifugal traction in the macula caused the fovea widening and thinning, potentially increasing the risk of macular disease^[17]. This may be one of the factors contributing to the observed gender disparity in the prevalence of MHs.

In our study, it was revealed an elevated incidence of hyperreflective lines or foveal crack lines in the fellow eyes of individuals, most of whom were with a larger size of FTMH and a broader and thinner macular fovea in the fellow eyes. This feature was located in the macula vertically in OCT images and was initially described in the natural course of acquired vitelliform lesions^[18-19]. The observed pattern maybe associated with the response to damage in various components such as photoreceptors, Müller cells, and/or the retinal pigment epithelium (RPE)^[20]. In our study, the patients exhibited hyperreflective lines in their OCT images all had experienced PVD in the macular zone. Complete PVD may serve as a crucial indicator for minimizing the risk of MH occurrence^[12].

Recent studies had highlighted that fellow eyes of patients with FTMH exhibiting a foveal crack sign may face a significantly elevated risk of deteriorating into FTMH^[21-22]. This risk escalated to nearly 70% or more when posterior vitreous adhesion was present^[22].

There were some limits of our study. It was difficult to ensure the same type of OCT equipment used in every hospital in multiple clinical study. There was reported inter-device agreement in OCT-derived of Heidelberg and Optovue in measuring retinal thickness measurements^[23]. In our cross-sectional study, it would affect little in the final results. In addition, limited number of participants in our study may have been insufficient; nevertheless, it proved to be sufficient to produce statistically significant conclusions.

In conclusion, it revealed the morphological alterations of macular region in fellow eyes of patients with idiopathic FTMHs detected by OCT. There were nearly 50% of the fellow eyes displayed various stages of MHs according to Gass classification. For the others, the feature of macular fovea exhibited a discernible trend characterized by an increased width and reduced height. OCT parameters of FFW and FFW/CFT ratio were good metrics for predicting MH. In the case of unilateral idiopathic MH, it was important to carefully monitor the condition of the fellow eye.

ACKNOWLEDGEMENTS

Foundations: Supported by Jiangsu Provincial Medical Innovation Team (No.CXTDA2017039); the Soochow Scholar Project of Soochow University (No.R5122001).

Conflicts of Interest: Li YT, None; Chen XZ, None; Lu YF, None; Liu YQ, None; Wu TH, None; Song ZY, None; Xie ZG, None; Lu PR, None.

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