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DISSERTATION

Functional Result of macular Hole Surgery

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Zusammenfassung

Hintergrund: Das Ziel dieser Studie war, die relevanten klinischen Faktoren, die optimale Methode und den Zeitpunkt des chirurgichen Eingriffs für Makulaforamen (MF) zu identifizieren.

Patienten und Methoden: In dieser Studie wurden 487 Augen von 451 Patienten untersucht, die einer Pars-plana-Vitrektomie (PpV) für MHs unterzogen wurden mit einem medianen Beobachtungszeitraum von 43,10±37,35 Monaten. Die MF wurden, basierend auf der zugrundeliegenden Pathogenese, wie folgt kategorisiert: idiopathisch (285 Augen); hohe Myopie (36 Augen); traumatisch (14 Augen); und Sekundär-Makulaforamen (152 Augen). Alle beobachteten Daten wurden an Hand von SPSS15.0 analysiert.

Ergebnisse: Die Erfolgsrate des Primäreingriffs in der jeweiligen Gruppe belief sich auf 88,1%, 86,1%, 64,3% und 96,1%. Die MF-Schließungsrate in der jeweiligen Gruppe betrug 97,5%, 100%, 92,9% und 98,7%,. Unter den vier Gruppen, mit Ausnahme der traumatischen MF-Gruppe, wurden die postoperativ bestkorrigierte Visus (BCVA) und die abschließend erzielte Visus (VA) im Vergleich mit de prä-operativen VA erheblich verbessert. Das Peeling der internen Begrenzungsmembrane (ILM) erbrachte keine höhere Erfolgsrate für den MF-Eingriff (MF-OP) oder die VA-Verbesserung, aber unter den Patienten mit IMF, war das Auftreten einer verringerten abschließenden VA in der ILM-Peeling-Gruppe niedrig. Eine ICG-Färbung in der SMF-Gruppe erzielte eine hohe Erfolgsrate für die MF-OP und hatte einen positiven Effekt auf die VA-Prognose in der IMF- und SMF-Gruppe.

Der Gebrauch biologischer Hilfsstoffe hatte keinen Effekt auf die Erfolgsrate des Primäreingriffs. Die die Erfolgsrate beeinflussenden Faktoren für die MF-OP und die postoperative Wiederherstellung der VA in den vier Gruppen waren unterschiedlich. ILM-Rest und postoperativ epiretinale Membranen (ERMs) waren die Hauptrisikofaktoren, die zum chirurgischen Misserfolg beitrugen. Kataraktchirurgie in Kombination mit synchroner oder asynchroner MF-Chirurgie hatte einen minimalen Effekt auf das Resultat der MF-Chirurgie.

Schlussfolgerungen: Unsere Studie legt nahe, daß ILM-Peeling und intra-operative ICG-Färbung wirkungsvolle Behandlungmodalitäten für die MF-OP sind. Chirurgische Fertigkeiten sollten jedoch weiter verbessert werden. Erfolgreiches und komplettes ILM-Peeling kann das Wiederauftreten von MF effektiv verringern, welches durch ERM aufgrund des ILM-Restes verursacht wurde, und die Wiederherstellung der postoperativen Sehfunktion schützen, indem sie Verletzungen am ILM-Gewebe reduziert. In Bezug auf MF im Stadium I-II, wenn die Beeinträchtigung der Sehfunktion nicht schwerwiegend war, sollten Patienten mit IMF und TMF beobachtet werden, während Patienten mit HMMF und SMF schnellsmöglich einem chirurgischen Eingriff unterzogen werden sollten.

Abstract

Purpose: The aim of this study was to identify the relevant clinical factors, optimal method, and timing of surgery for macular holes (MHs).

Patients and methods: This study reviewed 487 eyes of 451 patients who underwent pars plana vitroectomy (PPV) for MHs with a median follow-up of 43.10±37.35 months. The MHs were categorized as follows based on the underlying pathogenesis: idiopathic MH (IMH) (285 eyes); highly myopia MH (HMMH) (36 eyes); traumatic MH (TMH) (14 eyes); and secondary MH (SMH) (152 eyes). All of the observed data were analyzed using SPSS15.0.

Results: The success rates of the primary macular hole operation (MH-OP) in the four groups were 88.1%, 86.1%, 64.3%, and 96.1%, respectively. The MH closure rates in the four groups were 97.5%, 100%, 92.9%, and 98.7%, respectively. Among the four groups, with the exception of the TMH group, the post-operative best corrected visual acuity (BCVA) and final visual acuity (VA) were significantly improved in comparison with the pre-operative VA. Internal limiting membrane (ILM) peeling did not yield a higher success rate for MH-OP or VA improvement, but among the patients with IMH, the incidence of a decreased final VA in the ILM-peeling group was low. Indocyanine green (ICG) staining in the SMH group achieved a high success rate for MH-OP and had a positive effect on VA prognosis in the IMH and SMH groups. The use of biological adjuvants had no effect on the success rate of the primary operation. The factors influencing the success rate of MH-OP and post-operative VA recovery in the four groups were different. ILM rest and post-operative epiretinal membrane (ERM)

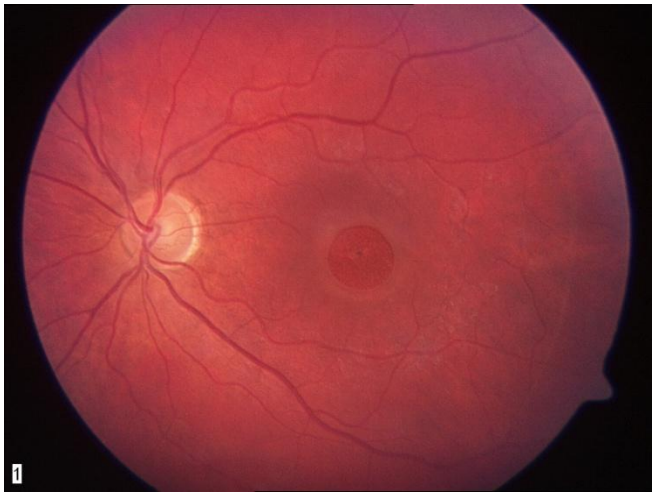
were the major risk factors contributing to the surgical failure. Cataract surgery, when combined with synchronous or asynchronous MH surgery, had a minimal effect on the outcome of MH surgery.

Conclusions: Our study suggests that ILM peeling and intra-operative ICG staining are effective treatment modalities for MH-OP, but surgical skills should continue to improve. Successful and complete ILM peeling can effectively reduce MH re-occurrence caused by ERM due to ILM rest and protect post-operative visual function recovery by reducing the injuries to ILM tissues. With respect to stage I-II MH, when visual function impairment was not severe, patients with IMH and TMH should be observed, while patients with HMMH and SMH should undergo surgery as soon as possible.

1. Introduction

1.1 Macular hole

A macular hole (MH) is a partial or full-thickness absence of the retina in the macula. A fully developed MH appears as a punched out, full thickness defect of retinal tissue involving the anatomic fovea (Fig. 1). MHs are a common cause of serious central visual loss, especially in the elderly.



The macula contains a full thickness hole which is about one disc in diameter (Fig.1).

1.2 History

A MH was first described by Knapp in 1869 in a German patient who sustained blunt trauma to the eye.[1] Subsequent case reports and series established MHs as a clinical entity. Two years later, Noyes reported a macular lesion in a 13-year–old girl secondary to blunt trauma, and provided the first accurate and detailed ophthalmoscopic description of a MH.[2] Noyes was perhaps the first to recognize that the lesion is characterized by a full-thickness defect in the retinal tissue at the center of the macula. In a review of 15 case reports of MHs published in the English literature in 1900, Ogilvie first developed the terminology, including *MH*, *floor,* and *edge* of the MH,[3] however, Ogilvie's description garnered little attention until almost a century later. Most of the earlier case reports involved young male patients with MHs secondary to blunt trauma, and therefore the lesion was customarily attributed to ocular trauma.[4-8] At the

beginning of the last century, more than 50% of all estimated cases of MHs were related to ocular trauma.[9]

Over the past century, however, ophthalmologists have recognized that MHs are more common in atraumatic settings and have differentiated the MHs from trauma-induced holes by describing them as idiopathic, full-thickness MHs. In 1900, Kuhnt first proposed that MHs were caused by cystoid macular degeneration, not necessarily related to trauma.[10] In fact, case series dating back to the 1970s reported that more than 80% of MHs were idiopathic and only less than 10% were associated with a history of trauma to the eye. In 1970, Aaberg reported that 9% of eyes with a MH were attributed to trauma.[11] However, in a 1982 series, 83% of MHs were shown to be idiopathic and only 15% were attributed to accidental or surgical trauma.[12] It is therefore essential to determine the etiology of MHs. In 1998, Ho compiled a historical timeline of MH theories (Table1),[13] elucidating the development of the lesion.

Table 1 Historical timeline of macular hole theories

Year	Author	Description
1869	Knapp	First case description of macular hole (traumatic)
1871	Noyes	First detailed clinical description of macular hole (traumatic)
1900	Kuhnt	Atraumatic theories of cystic retinal degeneration leading to macular hole
1901	Fuchs	Early histopathologic descriptions of macular hole including cystic retinal changes
1907	Coats	
1912	Zeeman	Histopathologic recognition of premacular vitreous condensation
1924	Lister	Vitreous forces and “vitreous traction bands” (anteroposterior) may cause macular holes
1967	Reese et al	Vitreous separation critical to macular hole formation
1982	McDonnell et al	Possible female hormonal influence on vitreous separation and macular hole formation
1983	Avila et al	Vitreous separation not necessary for macular hole formation
1986	Morgan and Schatz	Involutional macular thinning is a premacular hole
1988	Gass	Tangential vitreous traction and Gass biomicroscopic classification of Johnson premacular hole and macular hole lesions
1995	Gass	Centrifugal displacement of retinal receptors with umbo dehiscence Reappraisal of biomicroscopic classification of premacular hole and macular hole lesions

1.3 Hypotheses regarding the pathogenesis of different types of MHs

1.3.1 Traumatic macular hole (TMH)

Although trauma patients have a clear underlying etiology, including a history of blunt trauma to the eye and young age, the pathogenesis of TMH remains unclear. In the early 1990s, there were two hypotheses regarding the pathogenesis of TMH: blunt trauma causes deformation of the eye, leading to retinal expansion or a strong concussion ruptures the foveal retina; and a cystoid macular change following blunt trauma results in a MH. These theories were supported by the findings reported by Yamashita and co-workers,[14] who postulated two clinically and pathogenically distinct mechanisms of traumatic macular formation, depending on whether or not the posterior hyaloid was attached. One type of traumatic macular formations causes immediate visual loss due to primary dehiscence of the fovea. Optical coherence tomography (OCT) showed a retinal dehiscence with an intact posterior vitreousface. The other type of traumatic macular formation results in delayed visual loss due to dehiscence of the fovea secondary to persistent vitreofoveal adhesion.

1.3.2 Idiopathic macular hole (IMH)

Idiopathic macular hole is an age-related disease and is typically encountered in patients >65 years of age. IMH is especially common in women[15] during sudden changes in hormonal balance in the menopause, and following hysterectomy[12] and oophorectomy. In a retrospective analysis[16] of 300 consecutive cases of MH surgery, 2 of 8 (4.12%) women receiving tamoxifen therapy had bilateral MHs. Tamoxifen is a synthetic, non-steroidal, anti-estrogen compound that is widely used as an effective chemotherapeutic agent for the treatment and prevention of some forms of breast cancer. Comparison of the prevalence of MHs during tamoxifen therapy (4.12%) with the estimated percentage of women in the same age group in an Australian population on tamoxifen (0.82%) yielded statistically significant differences, suggesting a strong link between tamoxifen use and MH occurrence. In the 1970s and 1980s, many people believed that posterior vitreous detachment (PVD) played an important role in the

formation of MH. However, in 1988 Gass,[17] based on an analysis of a large sample of MHs, reported that only 12% of patients had PVD. Gass[17] speculated that anteroposterior vitreoretinal traction may not be the main cause of IMH formation, rather the occurrence of total PVD partly blocked IMH development. According to the Gass theory,[17-19] focal shrinkage of the foveal vitreous cortex results in tangential tractional forces acting on the fovea, thus leading to a foveal dehiscence that progresses from foveolar detachment to a full-thickness MH. OCT images assist in studies regarding MH pathogenesis.[19-24] The OCT studies demonstrated local posterior vitreous separation with persistent attachment of the vitreous to the fovea, which is termed perifoveal posterior vitreous detachment (PPVD). One study showed that the diameter of the vitreous attachment in eyes with PPVD correlates with induced changes in foveal anatomy, and deformation of the macula with eventual formation of a cystoid space within the fovea ultimately leads to a MH.[23] Indeed, the progress of IMH is related to enlargement of the PPVD;[25] however, vitreous traction cannot explain the range of clinical observations, such as MHs developing or even enlarging after non-surgical complete PPVD[26] or vitrectomy.[25] Cellular factors, such as glial cells and myofibroblasts,[27-29] also contribute to the development of vitreous traction. Despite similarities in the vitreofoveal configuration among women and men, there is a higher incidence of MHs in women.[15, 30-32] A genetic component may be involved, with a report indicating the occurrence of MHs among siblings within four families.[33] All of these observations suggest that mechanisms other than simple vitreofoveal traction maybe involved in the development of MHs.

1.3.3 Highly myopic macular hole (HMMH)

In high myopia, long axial lengths lead to retinal extension, resulting in extensive chorioretinal atrophy, especially RPE atrophy[34] in the macular fovea, and the co-existence of posterior staphyloma.[35-37] Progressive atrophy of choriocapillaris may increase degenerative changes, such as vitreous degeneration, linear rupture of Bruch's membrane, or intraretinal cysts. Vitreoretinal degeneration and intraretinal

cysts may lay the foundation for MH formation. PPVD is commonly observed in eyes with high myopia. Researchers have also observed that in the absence of a MH, PPVD might be related to vitreoretinal traction, staphyloma, and inward forces exerted by rigid retinal vessels and internal limiting membrane (ILM).[38]

1.3.4 Secondary macular hole (SMH)

Secondary macular holes are associated with an intraocular disorder. Albini et al.[39] and Donnio et al.[40] reported two separate cases involving a 10-year-old girl and an 11-year boy with a MH arising as a complication due to cat scratch disease. Although the mechanism was unknown, it was believed to be associated with partial vitreous detachment and a pre-existing subfoveal lesion, and likely representing an inflammatory focus. Kusaka[41] reported a case of a MH in high myopia following fungal endophthalmitis, with the authors speculating that vitreous inflammation may contribute to PPVD, which may lead to vitreoretinal traction resulting in formation of MH. MHs have also been reported as a rare complication of Behcet's disease,[42] von Hippel-Lindau disease,[43] intraocular nasal T/NK lymphoma,[44] and following ruptured retinal arterial macroaneurysm[45] and many other diseases attributed to cystoid macular edema, such as after cataract extraction,[46] toxoplasmic chorioretinitis,[47] posterior uveitis, diabetic retinopathy, intra-ocular inflammation, or retinal vascular obstructive diseases.

1.3.5 MH classification

In 1967 Reese et al.[48] proposed the significance of vitreomacular traction on the posterior vitreous surface in MH formation; however, the pathogenesis of MH has been controversial for decades. For the past 20 years, due to the technological development and application of OCT in ophthalmology and based on a large number of observations involving the subtle changes in the vitreomacular interface, we have a more profound comprehension about the pathophysiology, pathogenesis, natural course, and surgical intervention effect of MH. More and more evidence has shown that MH associated with

myopia or senile emmetropia belongs to the ‘primary’ disease caused by vitreous changes. It has been established that vitreous liquefaction, posterior vitreous adhesion, and traction are the major pathogenesis underlying myopia-associated MH. After birth, the gel state of the vitreous body liquefies with aging or myopia. After 40 years of age, vitreous liquefaction is more significant, while this process occurs 5-10 years ealier in myopia. The estrogen level change in females > 50 years of age may affect the content of hyaluronic acid, which accelerates vitreous liquefaction. The formation and expansion of the liquid cavity in the vitreous cavity, as well as dehiscence of the posterior limiting lamina of the vitreous, may affect the arrangement and direction of collagen fibers of the vitreous body on the ILM in the macular area. The original anterior-posterior distribution of collagen fibers changes to the distribution around the liquid cavity, which forms centrifugal traction in the macular area, increases the traction along the tangential direction, and finally causes the formation of a MH. In addition to vitreous liquefaction, the decrease in adhesion between the posterior vitreous cortex and the ILM is another cause of PVD, which is not always complete. More often, partial detachment occurs, with parafoveal detachment and foveolar attachment. This adhesion causes vitreomacular traction, including the distinctive macular fissural outer retinal thickening (foveal dehiscence), and results in a MH,[49,50] while for complete PVD, vitreous traction may also result in the hole at the posterior edge of the vitreous base. In recent years, some reports have proposed that some ‘secondary’ MHs are associated with partial PVD and posterior vitreous cortex traction examined by OCT, suggesting that vitreous changes play a certain role in the occurrence of a MH.

1.4 Stadium of MH

Johnson and Gass first described the classification system for MHs in 1988.[18] The classification, with its subsequent revision, is still currently used by clinicians and will be discussed below.

Normal fovea (Fig.2)

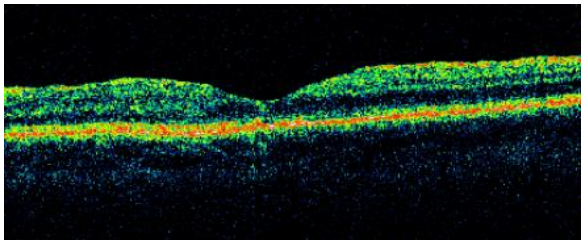


Fig.2

Stage 1a (Fig.3): Foveal detachment. Macular cyst. Tangential vitreous traction results the elevation of the fovea marked by increased clinical prominence of xanthophyll pigment. This stage is occasionally referred to as the yellow dot stage and can also be seen in cases of central serous chorioretinopathy, cystoid macular edema, and solar retinopathy.

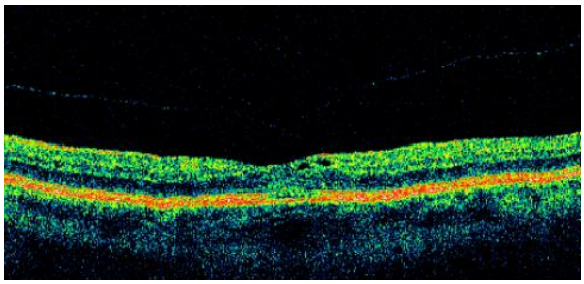


Fig.3

Stage 1b (Fig.4): As the foveal retina elevates to the level of the perifoveal, the yellow dot of xanthophyll pigment changes to a donut-shaped yellow ring. Persistent foveal traction leads to dehiscence of deeper retinal layers at the umbo.

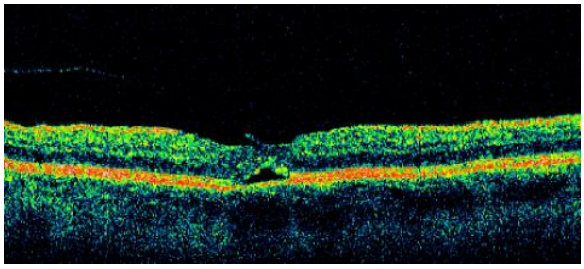


Fig.4

Stage 2 (Figs.5 and 6): This is the first stage when a full-thickness break in the retina appears. It is defined as a full-thickness MH< 400 µm in size. The full-thickness defect may appear eccentric, and there may be a pseudo-operculum at this stage if there has been a spontaneous vitreofoveal separation.

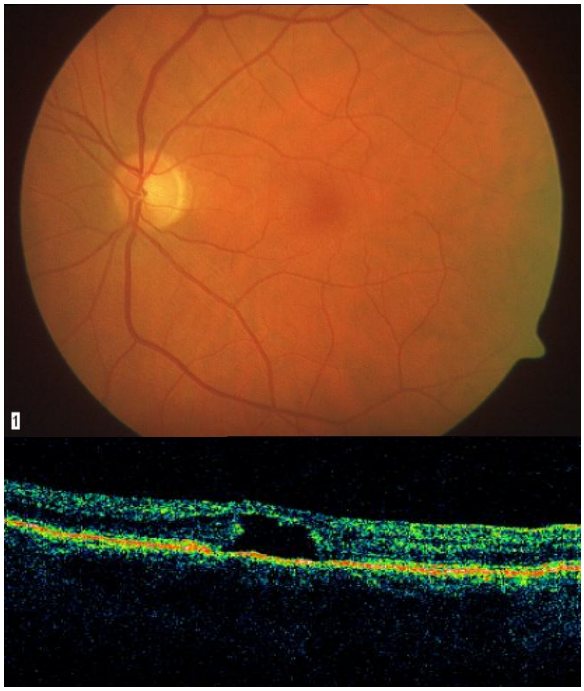


Fig.5 & Fig.6

Stage 3 (Figs. 7 and 8): A full-thickness MH in the retina is visible. It is > 400 µm in size and is still with partial vitreomacular adhesion/traction.

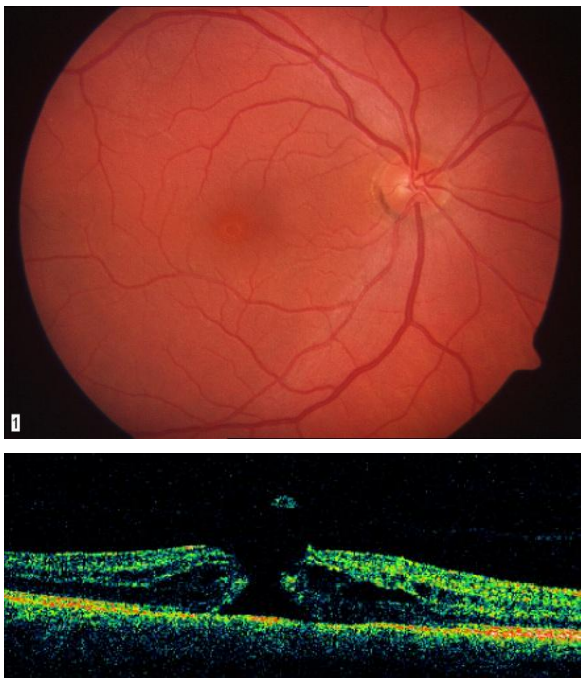


Fig.7 & Fig.8

Stage 4 (Figs. 9 and 10): A full-thickness MH is visible in the presence of a complete separation of the vitreous from the macula and the optic disc. There is recent evidence, however, that even in the presence of an apparent posterior vitreous detachment, a thin shell of residual cortical vitreous may still remain and contribute to the MH.

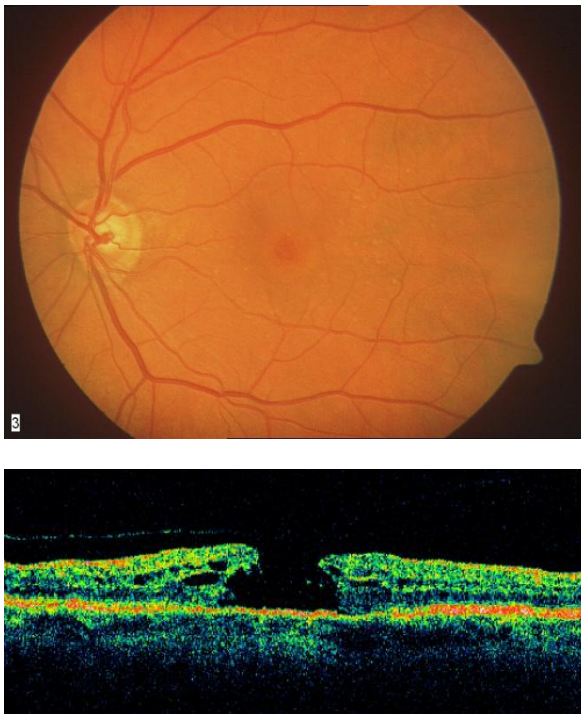


Fig.9 & Fig.10

1.5 Prevalence

Macular holes are infrequent in the population, as reported in previous studies (Beaver Dam Eye Study, Blue Mountains Eye Study, and Baltimore Eye Study[51-53]). The Beijing Eye Study reported that full-thickness MHs may be present in 1.6 of 1000 elderly Chinese in northern China. Thus, there would be approximately 750,000 patients with unilateral or bilateral full-thickness MH in the entire population of China.[30] The risk for a MH was calculated to be 0.17% for the population of southern India.[31]

1.6 Diagnosis

1.6.1 Clinical features

The macula is an area in which most of the photoreceptor cells are cones. The macula is responsible for visual acuity and color vision. Accordingly, damage to the macula leads to disorders of color vision and visual acuity. The diagnosis of a MH is made clinically based on altered morphology and function.

1.6.2 Examination of morphology

Using conventional methods (direct or indirect ophthalmoscopy, or a slit-lamp biomicroscope and a contact or handheld biconvex lens, such as a Goldmann three-mirror or preset lens), most patients with MHs can be diagnosed and classified; however, MHs can be confused with other disorders, and therefore such examinations provide only a subjective evaluation. In recent years, several clinical advances have improved the diagnostic accuracy for MHs.

1.6.2.1 Fundus fluorescein angiography (FFA)

During the initial stages of MH formation, no disorders are observed in the macular area; however, once the MH forms, an area of heightened fluorescence caused by loss of RPE that correlates with the size of the MH can be seen (Figs.11 and 12).

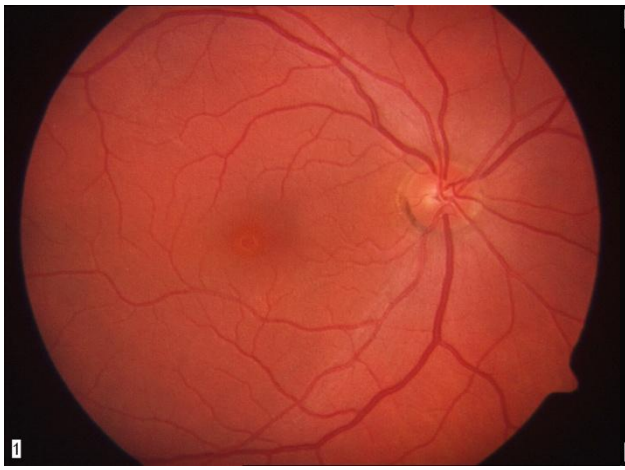


Fig.11

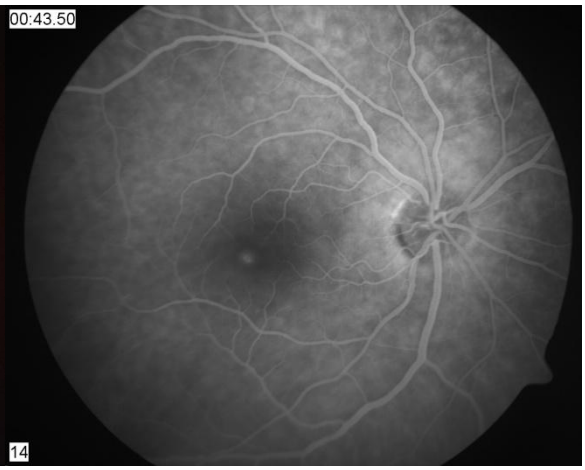


Fig.12

1.6.2.2 Scanning laser ophthalmoscopy (SLO)

A fundus camera is the main instrument for recording images of the fundus.[54] In 1980 Webb et al.[55] reported a method for imaging the retina using a laser. In 1987 Webb et al.[56] published a detailed discussion of the principles of confocal SLO, in which a highly collimated narrow beam of laser light is swept over the retina, delivering all of the energy to a very small spot for a very short period of time. The reflected light is detected on a monitor and synchronously decoded to form an image of the retinal surface of the deeper retinal layer in the macula. SLO, using an argon laser and a large confocal aperture, was useful in conducting kinetic examinations of the vitreous opacity above the macula (Figs. 13 and 14).

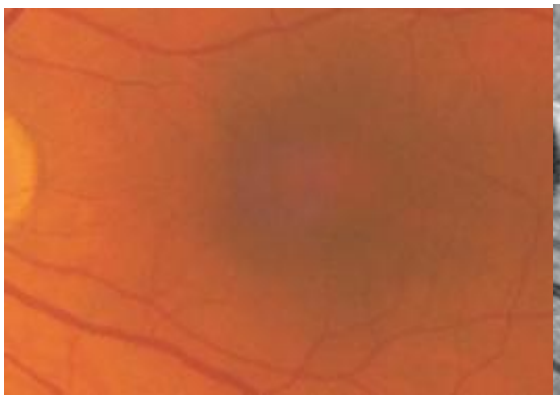


Fig.13 Fundus camera image of a MH.

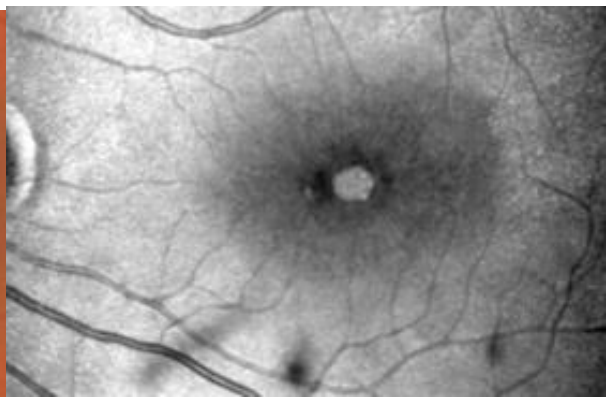


Fig.14 SLO infrared image of the MH shown in Fig. 13

SLO is helpful in differentiating holes from cysts. For example, a dense scotoma within the cyst area is indicative of a hole formation from the macular cyst. Using SLO, Acosta

et al.[57] evaluated functional changes and fixation behavior in patients with MHs and macular cysts. SLO can also differentiate between MHs and changes secondary to epiretinal membrane (ERM) formation.[58]

1.6.2.3 Confocal SLO

The Heidelberg retina tomography (HRT) is a new generation confocal laser scanning microscope (Heidelberg Engineering GmbH, Heidelberg, Germany) to aid in the acquisition and analysis of three-dimensional images of the posterior segment. The HRT facilitates the quantitative assessment of retinal topography and precise follow-up of topographic changes. HRT can also be used to analyze changes in MHs following vitrectomy and gas tamponade.[59]

1.6.2.4 Scanning retinal thickness analyzer

The retinal thickness analyser (RTA) is designed to detect glaucomatous changes, as well as macular pathologies at the posterior pole by obtaining a series of photographs, usually 16-24 photographic slits, in 1/2 of a second. A computer then combines the pictures into a photograph and a 3-dimensional image. This system can show retinal thickening, absence of a foveal depression, and elevation of the vitreoretinal surface. In a patient with retinal pigment epithelial detachments, the RTA can detect a relatively flat vitreoretinal interface, as well as an irregular chorioretinal surface.[60] In cases of suspected MHs and pseudoholes, the diagnosis was considered more reliable compared with conventional biomicroscopy. The extent of epiretinal membranes, the sites of adherence, and associated intraretinal cystic changes were identified.[61] Asrani et al.[62] reported that the findings of RTA support the idea that many MHs develop in association with intraretinal cystic changes.

Although both the RTA and HRT can provide additional information to clinically evaluate macular diseases, there are limitations.[63] For example, the image is adversely affected by media opacities, although the RTA is able to distinguish between different

retinal layers. The exact correlation between the histologic retinal layers and the various reflection layers in the RTA slit image has not been fully established. In normal conditions, a 3mm pupil is sufficient for HRT, but a narrow pupil size will affect the acquisition of the retinal image. Also, if the patient with a malignant myopia cannot fixate the target, it can be a challenge to obtain an ideal image.

1.6.2.5 Optical coherence tomography (OCT)

OCT was developed in 1991, first reported for observing macular diseases in 1995 by Puliafito,[64] then commercially introduced in 1996. OCT is a relatively new and non-invasive diagnostic modality that generates cross-sectional images of ocular tissues at the resolution of a micron *in vivo* and in real time, thus enabling a higher longitudinal resolution up to 5μm. This imaging technique uses low coherence infrared light, which is similar to ultrasound, to measure the echo time delay of light backscattering in tissue. Researchers and engineers around the world have worked to improve the image resolution and speed of OCT. The technique currently provides clear three-dimensional, volumetric imaging with extremely high voxel density and makes it possible to visualize the microstructure and pathology on par with MR imaging.[61] The introduction of frequency-domain/spectral domain/fourier domain OCT in 2006 greatly increased the resolution of retinal imaging. Thereafter, with the advent of ultra-highresolution optical coherence tomography (UHR-OCT), the axial resolution of OCT reaches 2-3μm; the transverse resolution reaches 10-15μm,[66] and even 5~10μm.[67] The high-data acquisition speeds enable high-density data sets with a large number of transverse positions on the retina, thereby reducing the possibility of missing focal pathologies. UHR-OCT is predominantly used for posterior segment imaging to measure retinal and macular thickness, and has been used to study and monitor diseases, such as vitreomacular traction, epiretinal membranes, MHs, and macular edema in diabetes, vein occlusion, and uveitis.[68,69] UHR-OCT is a valuable tool for differential diagnosis of a pseudo-MH (MPH) and lamellar MH (LMH) versus MH,[70,71] and in the precise stage classification,[19] therapeutic monitoring,[20] and prognostic

evaluation of surgical outcomes and post-operative restoration of macular microstructure.[72-80] In fact, lamellar macular defects can also be described with different subtypes of MPHs, LMHs, and foveal pseudocysts based on the OCT configuration and visual prognosis.[81] OCT scans are helpful in characterizing the quantitative defects with respect to base diameter, central foveal thickness, and the depth of the lamellar defect, and in scrutinizing the associated ERMs. OCT scans benefits also include study of the natural history of MH development of different etiologies[82] and surgical indications. With continuous development and popularization, OCT is not only used for the diagnosis and differential diagnosis of MHs, but also plays an important role in the pre- and post-operative management of MHs and other vitreomacular interface diseases.[75,83-85]

1.6.2.6 Fundus autofluorescence (FAF)

Although MHs are mainly confirmed by OCT, FAF is also helpful in the diagnosis and anatomic estimation of MHs. FAF is a simple and non-invasive diagnostic test, and may be especially useful in a setting in which OCT examinations are not readily available.[86] Markedly increased FAF in the foveal center corresponds to the MH, while a surrounding hypo-autofluorescent ring corresponds to the sub-retinal fluid cuff. The area of relatively reduced FAF around the ring corresponds precisely to retinal edema. A stellate appearance with dark radiating striae is seen in the relatively reduced FAF and correlates with intra-retinal cystic changes in the outer plexiform layer, observed using Fourier-domain OCT. The mean pre-operative visual acuity is significantly poorer in eyes without a stellate appearance than in eyes with a stellate appearance.[87] The stellate appearance in FAF is associated with earlier stages of MHs, better visual acuity at presentation, shorter duration of symptoms, and a more favorable prognosis.[88] FAF can also be used for the assessment of post-operative visual prognosis, Shiragami et al.[89] studied the FAF signals at closed maculas with SD-OCT and visual prognosis after successful surgery in eyes with full-thickness IMHs, and

concluded that patients with increased FAF signals at closed maculas might have a better visual prognosis post-operatively.

1.6.2.7 Application of adaptive optics (AO) in retinal imaging technology

Due to the structural characteristics of the biological tissues of eyes, the higher order aberration of eyes is more complex than any other optical system, and is dynamic, which restricts the high-definition imaging of the aforementioned retinal imaging technologies in early years. This situation was improved with the application of AO in visual optics.[90-92] The appearance and further development of the adaptive optical fundus camera,[93] the Scanning Laser Ophthalmoscope (SLO),[94-96] OCT[67,97] and FFA continuously demonstrate high-definition *in vivo* retinal imaging. Cense et al.[98] successfully applied super luminescent diode and femtosecond laser in AO-OCT and obtained high-definition retinal imaging. Zawadzki et al.[99] combined AO-OCT with AO-SLO. The two modes of imaging utilize different detection systems, resulting in more comprehensive insight into the morphology and potential function of the retina and obtaining ultra-high definition retinal images. The continuous renewal of technical equipment has led to convenience in the observation, diagnosis, and treatment of MHs.

1.6.3 Examination of visual function

a. Central visual acuity (VA [distance/near vision]) reflects the visual sensitivity of the macular fovea.

b. Contrast sensitivity is the ability of the eye to discern subtle degrees of contrast. Contrast sensitivitymay become abnormal before central visual acuity is affected in some macular diseases.

c. Color vision may also be a sensitive indicator of acquired macular disease.

d. The Amsler grid is used to test the central 20 degrees of the visual field. The Amsler grid is a speedy, effective, and sensitive way to test the central visual field.

e. Watzke test. A thin long beam of light is projected through a 78 or 90D onto the MH and the patients are asked if they notice a gap in the light. The presence of a gap or a positive Watzke's test occurs in full thickness MHs.

f. Microperimetry.The retinal function in the macular region before and after IMH surgery is assessed with microperimetry and fERG[100]. The BCVA assessment index only reflects the function of macular fixation points and the OCT examination only reflects the anatomic structure of the macula and cannot reflect functional recovery. Studies indicate that normal and abnormal macular morphology after surgery has no significant difference in vision changes before and after surgery. Only a few cases of abnormal macular morphology are associated with visual prognosis after surgery. The foveal sensitivity tested by microperimetry reflects the function of the entiremacular region.[102, 103]

g. Multifocal electroretinogram (mfERG). This examination can enhance the spatial resolution of the visual function assessment, and can objectively, non-invasively, and quantitatively assess the visual function of the posterior pole, especially the macula, and can localize the specific area and distribution of retinal damage.[104,105] Thus, a mfERG is important in the accurate assessment of visual function recovery after MH surgery. It has been reported that 1 year after a vitrectomy, a mfERG shows that the amplitude density is significantly increased within the central 9 degrees of the macula, of which the amplitude density increased by approximately 80% within the central 2.8 degrees of the macula and increased by approximately 30% within 2.8~9 degrees. It was objectively assessed that retinal function in the macular region and near the macular region was significantly increased.[106]

1.7 Treatment

In 1988 Johnson and Gass[18] first described anteroposterior and tangential vitreous traction on the fovea as a primary underlying cause for idiopathic MHs, and in 1991 Kelly and Wendel[107] first described vitrectomy for MHs. Since then, a standard three-port pars plana vitrectomy (PPV) has been widely used for MH therapy. In

standard MH therapy currently, including PPV, the posterior hyaloid is detached from the macula, intra-ocular gas tamponade is established, and face-down positioning for up to 2 weeks yields 70%～80% MH closure and 55%～60% vision improvement. With advances in research, promising therapies are developed.

1.7.1 Improvement of surgical instruments

Thirty years after the advent of vitrectomy, vast improvements in technological sophistication have paved the way for the development of novel and efficient surgical designs that reduce scleral incision injuries, and promote the spontaneous healing of surgical wounds and patient recovery. For example, the 25-(25G),[108] 23-(23G),[109] and even 27-gauge (27G) vitrectomy instruments[110] have replaced the traditional 3-cut 20-gauge (20G) instruments. With the help of a wide-field inversion lens system, use of the new microsurgery instruments, including a high speed cutter, ILM forceps, and microforceps facilitates trans-conjunctival sutureless vitrectomy surgery.[108] The application of intraoperative OCT[111] in recent years has created a new viewing angle during MH surgery. Compared with the conventional 20G vitrectomy, 25G and 23G trans-conjunctival sutureless vitrectomy is characterized by a small wound, a short operative time, and a rapid post-operative recovery. Moreover, the 23G system compensates for the defects of the 25G system and combines the advantages of the 20G and 25G systems, with higher cutting efficiency, harder instruments, and brighter lighting, which elevates MH surgery to a higher level. It has been reported, however, that 23G PPV shortens the operative time, alleviates post-operative complications, and reduces patient discomfort, but the post-operative efficacy and safety are not better than a conventional 20G vitrectomy.[112]

1.7.2 Internal limiting membrane peeling (ILM peeling)

In the mid-1990s, several published reports discussed the use of PPV to treat IMH; however, 20~30% of the IMH cases are still clinically unclear. Researchers engaged in IMH clinical research have shown the following: IMHs are enlarging, even in stage III

and IV IMH with total PVD, considering that ILM might be the only tractive force; with respect to IMH after PPV, despite missing vitreous cortical traction, the holes remain open and some of occur in macular detachment and it is thought that Müller cells take the ILM as support to proliferate and cause vitreoretinal traction; and Yoon[27] evaluated surgical specimens of the ILM of the retina and epiretinal tissue overlying and surrounding the MH with transmission electron microscopy and showed that tissue from stage 2 holes showed cellular elements enmeshed in cortical vitreous, while tissue from stage III and IV holes had cellular proliferation on the ILM. Cells, including RPE and glial cells with myofibroblastic differentiation, were present in areas with cellular proliferation. IMHs appear to develop from contraction of the pre-foveal vitreous, and the hole enlarges because of the tangential contractile forces generated by RPE and glial cells that migrate onto the inner surface of the ILM. In 1994 Morris[113] first proposed that removal of the ILM is helpful in the treatment of tractive macular diseases. During the late 1990s researchers initiated clinical studies of ILM peeling to treat IMH. In 2000 Mester and co-workers[114] reviewed 36 related studies in which 221 cases underwent ILM peeling, and the MH closure rate reached 96% and the vision improvement rate was 81%, which was higher than the closure rate of 81% and vision improvement of 60% without ILM peeling. The face-down posture maintenance time was also shortened from 10 to 4 days, and the hole recurrence rate was also reduced.[115] Some researchers reported that surgery with ILM peeling may improve reading vision.[116] It is now widely accepted that removal of the ILM as an adjunct to vitrectomy improves anatomic hole closure following MH surgery.[117-119]

A recently published meta-analysis[120] also supported ILM peeling as the surgical procedure for stage II, III, and IV full-thickness MHs. It has been reported[121] that donut-shaped ILM peeling with ILM reserving within 400μm of the foveola for stage II MH had better MH repair and vision recovery than whole ILM peeling. The study reported that non-peeling of the foveolar ILM in early stage II IMH surgery prevented inner retinal damage, restored the umbo light reflex, achieved better foveolar microstructure, and led to better final visual acuity. Despite the clear indication in MH surgery, ILM peeling is a traumatic procedure that has acute effects on the underlying

inner retinal layers.[122]

1.7.3 Dye-assisted ILM peeling

Because the ILM is thin and transparent, it is not always easy to separate and completely remove. It is always technically challenging in that the difficulties revolve around the initial peeling step in distinguishing between peeled and unpeeled ILM and determining the extent of ILM peeling. Improper peeling can lead to irreversible retinal damage, even in the hands of a skilled and experienced surgeon. Kadonosono[123] first reported ILM peeling with indocyanine green (ICG) staining, which makes the procedure faster and easier to perform. Staining with trypan blue (TB)[124,125] can also yield good results. In 2000 Peyman and co-workers[126] reported application of triamcinolone acetonide (TA) during vitrectomy. The white particles of the TA suspension adhere to the surface of the residual vitreous cortex on the ILM or to the ILM itself, and the peeled area of the membrane can be confirmed by the lack of white particles; however, some *in vitro* and *ex vivo* experiments, as well as clinical reports, suggest dye toxicity to the retinal pigment epithelium (RPE) and worse visual outcomes with the use of dyes.[127-129] Especially for ICG, there aremany reports on the toxic effects of ICG staining in recent years because ICG is widely used. Rodrigues et al.[130] published a review after referring to the relevant literature published between 1998 and 2005, and suggested that the following methods might be used to minimize toxic effects: dye injection in concentrations as low as possible; avoidance of repeated ICG injections onto bare retina; dye injection far from the MH to prevent direct dye contact with the RPE; short incubation time of ICG in the vitreous cavity to diminish the concentration in contact with the retinal tissue; and the light pipe kept far from the retina throughout the entire surgical procedure. Researchers have reported the use of infracyanine green (IFCG)[131] in the belief that ICG contains iodine, which must be dissolved in distilled water to obtain a hypo-osmolar solution. IFCG does not contain iodine, and thus can be dissolved in 5% glucose to form an iso-osmotic solution compared with ICG. Thus, it is speculated that IFCG may be safer than ICG because of

the absence of hypo-osmolar toxicity. Similar reports[132-136] have also pointed out that when TA replaces ICG and TB, retinal toxicity is greatly reduced, and therefore might be a safer and less expensive intervention. In 2006 Enaida and colleagues[137] first reported the use of 0.25mg/ml of Brilliant Blue G (BBG) solution as an auxiliary stain, and pointed out that BBG at this concentration selectively stains the ILM and does not stain the ERM. Shukla et al.[138] compared the application convenience of BBG, TB, and ICG in IMH surgery and the effect on post-operative efficacy, and pointed out that the effect of BBG and TB on the prognosis of post-operative visual acuity was significantly smaller less than ICG, while the ILM staining effectiveness of BBG was similar to ICG. In recent years, there are more and more reports suggesting that the prognosis of visual acuity with BBG dye-assisted ILM peeling is better than ICG.[139,140]

1.7.4 Inverted ILM flap technique

The inverted ILM flap technique[141] was first published in *Ophthalmology* in 2010. Michalewska and colleagues[141] performed surgery on 50 eyes of 46 patients with large MHs (>400μm) using this new technique and obtained a 98% hole healing rate compared to an 88% hole healing rate with conventional surgery. During the 1-year follow-up after surgery, the recovery in visual acuity was better than the conventional surgery group.[142] Shin and colleagues[143] described the perfluoro-n-octane (PFO) -assisted single-layered inverted ILM flap technique. A true flap is covered on the MH and the assistance of PFO makes the flap difficult to displace, solving the operation failure caused by flap displacement during fluid-air exchange. PFO has a low vapor pressure, and thus can be removed by evaporation without lavage, which might displace the flap.[143] The inverted ILM flap technique may close the chronic large MHs, but post-operative RPE atrophy is expanded.[144]

1.7.5 Use of adjunctive agents

To raise the safety and effectiveness of treatment, to enhance the anatomic closure rate, and to improve visual outcomes, many different adjunctive agents, such

as transforming growth factor-β2 (TGF-β2),[145-147] serum,[148] autologous platelet concentrates,[149-151] thrombin,[152,153] an autologous plasma-thrombin mixture,[154] and autologous whole blood[155] have been used as sealants in MH surgery. In 1992 Glaser and co-workers[145] first reported that local application of TGF-β2 at the edge of the MH can reproducibly induce flattening of the surrounding neurosensory detachment. Glaser and co-workers[145] believed that when the MH closure rate reaches 90%, TGF-β2 can increase the adhesion between retina and choroids simultaneously to stimulate the regeneration of photoreceptors. With the increase in the TGF-β2 concentration, the retinal anatomic closure rate increased and vision improvement was more apparent.[146, 147] The process of extraction and preservation of TGF-β2 is complex, and not clinically feasible. Autologous serum containing platelet-derived growth factor (PDGF), transforming growth factor (TGF), and fibroblast growth factor (FGF) are compatible with allogenic antigen. Liggett[148] reported the application of autologous serum combined with current surgical techniques in treating stage III or IV MHs to achieve a MH closure rate of 100%. In 1995 Gaudric and associates[149] were the first to use an autologous platelet concentrate to seal a MH. The results suggested that an autologous platelet concentrate could significantly improve the success rate in MH surgery. Gaudric et al.[149] believed that blood platelets have wound healing functions. An abundance of growth factors, such as TGF-β2, with the aforementioned physiologic benefits, as well as the ready availability of autologous platelet concentrates have wide clinical applications. Thrombin[153] has also been used in MH treatment, but a sterile hypopyon occurred post-operatively that might be related to the xenogenous antigenicity of bovine thrombin. Furthermore, autologous whole blood cannot be recommended as an alternate adjunct for the treatment of MHs without membrane removal.[155]

1.7.6 Selection of intra-ocular tamponade

Tamponade facilitates filling of the vitreous cavity based on surface tension, buoyancy, and spatial occupation to support the separated retina inside the eyeball and

seal the MH, and prevent fluid entering the hole can result in adherence of retinal neuro-epithelium to pigment epithelium, spur the multiplication of neuroglia cells, and growth and contraction of epiretinal membrane, resulting in closure of the MH. These tamponades include air,[156, 157] SF6,[158] C2F6,[155,159] C3F8,[160,161] and silicone oil.[161,162] Kelly and Wendel[107] applied SF6 as a gas tamponade in the study of MH treatment and reported a 73% MH closure rate. Subsequently, research showed that using the same gas tamponade (SF6,[158] even a shorter acting gas-air[156,157]) increased the closure rate significantly (> 90%). Almost one-third of all ophthalmologic surgeons choose SF6 in MH surgery.[163] Whether or not the use of a stronger and longer acting gas, such as C2F6, C3F8 can enhance the success rate of the primary surgery is still a matter of debate. Kim and associates[164] indicated that MH surgery using SF6 gas yields similar results as those obtained with C3F8 gas and may be a good option. Not all of the MHs can be sealed after primary surgery. For example, Iwase and Sugiyama[165] applied SF6 tamponade in the second surgery and asked the patients to maintain the face-down posture for 12 h daily until the MH was closed. The result suggested that following the gas tamponade again, the mean time of MH closure was 4.1days. Iwase and Sugiyama[165] therefore indicated that C3F8 tamponade was not necessary for MH surgery, and its long half-life in the eye might be disadvantageous. C3F8 gas proved to be a more effective tamponade than silicone oil. Lai and associates[161] indicated that although the final rate of MH closure was similar between the oil and gas groups (90% vs. 96%), the eyes receiving oil tamponade required significantly more repeat surgeries. The rate of MH closure following one operation with oil tamponade was significantly lower than gas tamponade (65% vs. 91%), and the final median visual acuity for the gas group was significantly better than the oil group (20/50 vs. 20/70). Silicone oil tamponade especially benefits posterior staphyloma-associated MH in highly myopic eyes,[162] eliminates the need to position patients face-down post-operatively, and is also beneficial to patients traveling by air.

1.7.7 Face-down position (FDP)

To keep the FDP for 7-14 days after surgery was once the standard practice in MH repair; however, whether or not the strict compliance with this standard is really needed is controversial.[166,167] Tornambe et al.[168] first reported the fairly good post-operative effect after MH repair without FDP in 1997. A pilot randomized controlled trial[169,170] indicated that the FDP was beneficial to the repair of MHs>400μm and had no obvious effect on the repair of MHs<400μm. Forsaa et al.[171] pointed out that short-term post-operative non-supine positioning and strict FDP had no different effect on post-operative healing. According to the review of previous reports, even the large MHs do not benefit from the strict FDP. MH surgery with broad ILM peeling and no FDP also achieved a fairly ideal surgical curative effect.[172]

1.7.8 Enzymatic Vitreolysis

Oriplasmin (JETREA®; ThromboGenics NV, Leuven, Belgium)[173,174] is a recombinant human serine protease with activity against components of the vitreous and vitreoretinal interface (e.g., fibronectin, laminin, and collagen). The recommended dose of a single 125μg intravitreal injection is indicated for the treatment of symptomatic vitreomacular adhesions (USA) and vitreomacular traction including when associated with MHs with a diameter≤400μm in adult patients (EU).

The availability of oriplasmin was a major advance in the treatment of MHs. This drug has not been popularized for various reasons, but the utility of oriplasmin in the treatment of MHs is supported by existing clinical studies and the literature. When surgery is considered to treat stage I and II MHs, a more convenient and safe method may be used to thwart the progression of MHs through intravitreal injection and better protect visual acuity; thus, the latter should be a better treatment choice.

1.8 Complications following vitrectomy surgery for MHs

Although patients undergoing eye surgery are at risk for complications, some of the complications are exclusive to MH surgery. The complications may include anomalies of the RPE, retinal detachment, macular cystoid edema, choroidal neovascularization,

endophthalmitis, re-opening of the MH, intraocular pressure elevation, visual field defect, cataracts, and retinal phototoxicity.

1.8.1 Defects or abnormal changes in the RPE

Several reports have suggested that changes in the RPE after MH surgery can reach 33%.[175, 176] These local changes in the RPE are thought to be related to prolonged FDP and light damage. In the past, most researchers thought that the abnormalities in the RPE were caused by phototoxicity; however, Charles[177] believed that the abnormalities in the RPE were only due to damage caused by surgery. Charles[177] observed that the damage to RPE and photoreceptors only occurred after surgery combined with drainage of a substantial amount of subretinal fluid. Pigment loss or abnormalities interfered with the photoreceptor function, resulting in impairment of visual acuity. In recent years, however, the application of surgical dye, especially ICG, has been the focus of attention of most reports. Engelbrecht and associates[178] reported that of the 21 eyes that underwent ICG-assisted ILM peeling to treat MHs, post-operative RPE changes were noted within the macula in 12 eyes. Of the 12 eyes, 10 were shown to have atrophic changes in the RPE within the area of the previous MH. Two eyes had RPE changes outside of the fovea in the area of the initial incision of the ILM with the microvitreoretinal blade. Uemoto et al.[179] suggested that the use of ICG dye with illumination may increase the risk of RPE damage and secondary choroidal and foveal morphologic changes.

1.8.2 Retinal detachment (RD)

According to several authors, RD after MH surgery is the most frequent and serious complication of macular surgery, with varying incidence. Guillaubey and associates[180] reported 634 eyes that underwent macular surgery procedures with a minimal follow-up of 1 year. In the case of patients undergoing IMH (n = 272) and ERM surgery (n = 362), Guillaubey and associates[180] reported that the rate of RD occurring after IMH surgery was higher than after the ERM surgical procedure (6.6% vs. 2.5%; p = 0.02).

The rate of RD was higher in patients presenting with stage II and III IMH than stage IV IMH. Guillaubey and associates[180] speculated that surgical detachment of the posterior vitreous surface and associated peripheral retina anomalies may increase the rate of this complication. Banker and Freeman[175] reported an incidence of 11% occurring 2-15 weeks after surgery, with a mean of 6 weeks. The macular fovea was involved in one-half of the RD cases, with greater than half of these cases presenting with inferior peripheral retinal tears and detachment. Park[176] reported that the incidence of rhegmatogenous retinal detachment (RRD) from a peripheral retinal break after vitreous surgery for MHs was 14%. Compared with the macular pucker group, vitreous surgery by the same surgeons resulted in posterior segment complications, in particular a significantly higher rate of peripheral retinal tears and detachments (P < or = 0.05). Tabandeh and associates[181] reported RD in 8 (1.8%) of 438 eyes undergoing MH surgery. The rate of RD was 3.5% early in the course of the surgeon's experience (first 200 cases) and 0.4% later in the surgeon's experience (after 200 cases; P = 0.026). Park[176] and Tabandeh and associates[181] opined that this complication may be related to posterior cortical vitreous stripping. Surgeons[180] suggested that careful examination of the peripheral retina is critical in preventing RD occurring after macular surgery.

1.8.3 Cystoid macular edema (CME) and intra-ocular infection

CME develops as a result of cataract extraction after MH surgery. Huynh and Johnson[46] reviewed six eyes of six consecutive patients who had successful MH repairs and subsequently developed CME. CME developed after cataract extraction in five eyes and after MH surgery in one eye only. The average time from MH surgery to diagnosis of CME was 11.2 months (range, 2.5-23.0 months). The average duration of CME was 5.5 months (range, 1.5-17.0 months). Five (83%) of 6 eyes had sustained closure of the MH throughout a mean follow-up period of 31.8 months (range, 9.5-62.0 months). Patients were treated with topical anti-inflammatory therapy, and all had resolution of CME. Huynh and Johnson[46] speculated that in most eyes the reparative

mechanisms involved in MH closure confer sufficient strength to withstand the tensile forces associated with CME.

1.8.4 Choroidal neovascularization (CNV)

There are few reported cases of CNV developing after MH surgery. About 1% - 3% of patients who undergo MH surgery can develop choroidal neovascularization membranes (CNVMs),[175, 182] even 6 months after surgery. The pathogenesis of CNV following MH surgery may include age-related degenerative changes in Bruch's membranes, RPE abnormalities, inflammatory processes, or surgical trauma.[183]

1.8.5 Endophthalmitis

Banker and Freeman[175] and Park and associates[176] reported that the incidence of endophthalmitis is 1%. Smiddy[184] reported a higher incidence, which was attributed to the use of an autologus blood product as an adjunctive agent. It was also believed that some adjunctive agents may increase the incidence of endophthalmitis, such as 10% sterile hypopyon after the use of bovine thrombin.[153]

1.8.6 Re-opening and enlargement of MHs

Several studies have reported different MH re-opening rates with variable follow-up. Paques et al.[185] reported that MH re-opening occurred in 9.5% of cases (11 of 116). Paques et al.[185] speculated the cause of re-opening might have been anatomic stress, such as epiretinal membrane formation or macular edema. An association between cataract extraction and re-opening of MHs has been considered, but no causal connection between the two has been shown. Christmas et al.[186] reported 17 of 353 patients (4.8%) in whom MHs re-opened after initial successful surgical closure. Twelve eyes underwent re-operation and 10 eyes had undergone cataract surgery between two MH procedures, but in only 1 eye did the re-opening appear to occur in association with the procedure; however, Bhatnagar and associates[187] reported a retrospective, comparative, consecutive case series with a mean follow-up of 26.6 months involving

211 eyes, which were divided into the following 4 groups: group 1, prior cataract extraction, 56 eyes; group 2, vitrectomy followed by cataract extraction, 86 eyes; group 3, vitrectomy only, 41 eyes; and group 4, vitrectomy and cataract extraction as a combined procedure, 28 eyes. Twenty-four MHs re-opened (11%) and the greatest number of MH re-openings (17 [20%]) were in group 2. Cox analysis showed a 4-fold increased risk of re-opening in group 2 eyes. Eyes with CME after cataract extraction had a 7-fold increased risk of MH re-opening. Kaplan-Meier analysis showed increased rates of MH re-opening in group 2 eyes compared to the other 3 groups combined.

1.8.7 Intra-ocular pressure elevation

Elevation of intra-ocular pressure is a significant complication after MH surgery, even without adjunctive therapy, and usually occurs within the first post-operative week. In most cases, elevated intra-ocular pressureis transient and can be controlled by medication.[188] Thompson et al.[189] indicated that there is no statistically significant difference in the risk of increased intra-ocular pressure in eyes treated with short-, intermediate-, or long-duration gas tamponade, but is markedly increased in eyes in which recombinant TGF-β2 is used as an adjunctive agent for MH surgery. Impurities in recombinant TGF-β2 may explain the relatively high risk of increased intra-ocular pressure.

1.8.8 Visual field defects

Boldt et al.[190] reported that 7% of patients treated with vitrectomy and gas-fluid exchange for MHs have visual field defects. The most common visual field defect is dense and wedge-shaped and involves the temporal visual field. Although unclear, the etiology may involve trauma to the peri-papillary retinal vasculature or nerve fiber layer during elevation of the posterior hyaloid or during aspiration at the time of air-fluid exchange, followed by compression and occlusion of the retinal peri-papillary vessels during gas tamponade. Another study[191] showed that the cause for visual field defects following vitrectomy and gas-fluid exchange for MHs is unclear; however, a reduction in

the nerve fiber layer thickness from the superior and nasal peri-papillary area suggest that acute surgical release of the posterior hyaloid and the use of long-acting intra-ocular gas in certain patients may result in visual field defects. Arima et al.[192] reported a 22% incidence of visual field loss after MH surgery. The thickness of the retinal nerve fiber layer was measured post-operatively to determine whether or not any damage to the optic nerve head occurred during surgery; however, no conclusive evidence regarding the pathomechanism of the MH surgery-associated visual field loss was obtained. Arima et al.[192] indicated that this complication is variable in severity and is usually permanent. Kokame[193] concluded that air-fluid exchange can cause visual field defects post-operatively. In recent times, an increasing number of researchers[194-196] believe that the visual field defects must be related with the use of ICG dye, and speculate that visual field defects, specifically nasal defects, can occur after MH surgery with ICG-assisted ILM peeling. The incidence of visual field defects depends on the concentration of the ICG solution and/or the contact time with the retina and the enhanced toxicity of ICG resulting from the exposure to illumination.

1.8.9 Cataract

Although vitreoretinal surgery for MHs has been refined over the last two decades, progression of nuclear sclerotic cataracts remains a complication of this procedure that occurs almost universally in phakic eyes. Ho et al.[13] indicated that progressive lens opacification is the most common surgical complication in phakic patients. Scott and associates[197] reported a mean follow-up of 91.0 months after MH surgery in 74 eyes, 62 eyes of which had cataract extraction performed at a median of 13.9 months after MH surgery. Thompson[198] used a scale from 0-4.0 to grade nuclear sclerotic cataracts and posterior sub-capsular cataracts before and after vitrectomy. In the study of 202 eyes with MHs, 80eyes with epiretinal membranes and 19 eyes with vitreomacular traction syndrome, Thompson[198] found that nuclear sclerotic cataracts had a minimal increase after vitrectomy in patients < 50 years of age. Patients > 50 years of age, including 50-60 years, 60-70 years, 70-80 years, and 80+ years, showed a similar

rate of increase in nuclear sclerotic cataracts that was independent of age. The rate is approximately 6-fold greater than in patients < 50 years of age. Furthermore, intravitreal gas tamponade is associated with an increase in nuclear sclerosis of approximately 60% compared with eyes without the use of a gas tamponade. Wu and associates[199] reported a case series of 13 pediatric patients 1-15 years of age with traumatic MHs undergoing surgical repair with a mean follow-up of 12.5±16.4 months, in which only one eye was observed to develop a posterior sub-capsular cataract after surgery. The findings of Wu and associates[199] were consistent with another study[13] showing that the incidence of this complication was lower than that associated with vitrectomy in the adult population.

1.8.10 Other complications

Arevalo and Garcia[200] reported an accident that occurred during surgery in which subretinal ICG was accidentally introduced through the MH, and an iatrogenic macular retinal tear though the papillomacular bundle was created because at the beginning of the instillation the ICG was pushed with too much force into the vitreous cavity with a 20-gauge cannula.

2. Purpose of the study

With the continuous appearance of various precise inspection equipment and surgical equipment for ophthalmology, we have a further understanding regarding the connection between the vitreous body and MHs. In addition, the assessment of the anatomy and function of the macular region is more objective, direct, and convenient, and the degree of surgical precision is also continuously improved; however, in economically underdeveloped areas, due to the restrictions in medical conditions, the diagnosis and treatment on MHs are far less than developed areas. Thus, experience in previous surgical diagnosis and treatment is of more guiding significance in the clinic, especially for the surgeons just starting to perform this surgery.

In 1991 the first published report[44] on MH vitrectomy addressed the following two

questions: (1) Is it possible to re-attach the retina around the MH? And (2) If the retina is re-attached, will the patient's central vision improve? At the time, the patients had a 58% hole closure rate, with 42% of all patients reporting an improvement in visual acuity of two lines or better. After > 20 years of practice and research, the answers to these two questions are obvious. With the help of vitreous surgery and other improved surgical techniques, the retina around the MH can be re-attached and the hole can be closed in >90% of the cases, with a vision improvement >80%,[113, 115] along with a lower re-opening rate. The subject of our study was to determine why patients with similarly classified MHs have different prognoses post-operatively, why some of the patients who had perfect MH closure still had no improvement in visual acuity, and why some of the MHs remained open or re-opened after one or more surgical interventions.

This study focused on clinical factors, surgical outcomes, complications, and prognostic factors of MH surgery. We propose to answer the following questions:

1. Which clinical features can influence surgical results and complications?
2. What is the optimal technique and timing of surgical treatment for MHs with difference causes?

3. Materials and methods

3.1 Patients

This study reviewed consecutive case series, including 824 eyes of 753 patients who underwent PPV for MHs between June 1994 and July 2008 in the Department of Ophthalmology of Charité Medical University Hospital Benjamin Franklin in Berlin. The original notes of all the cases were reviewed, and the below data were recorded. To attain a longer follow-up time and more intact records of the cases, standard letters and questionnaires were sent to the patients' ophthalmologists. If the patients changed ophthalmologists or the ophthalmologists could not be contacted, the letters and questionnaires were sent to the patients and the new ophthalmologists completed the questionnaires. A total of 770 letters and questionnaires were sent, 594 (77%) questionnaires were returned, and 480 questionnaires (62%) recorded a longer follow-up time than at our hospital. A follow-up period of < 3 months was excluded as were the cases without complete data. Patients with a history of diabetes mellitus, intra-ocular surgery predating the development of MHs, glaucoma, uveitis, ocular tumors, maculopathy, and amblyopia were then excluded. The study ultimately comprised a total of 487 eyes in 451 patients for data analysis.

3.2 Collection of patient data

3.2.1 General clinical data

All of the cases were recorded, includding names, dates of birth, gender, course of disease, cause of disease, dates of surgeries, and duration of follow-up.

3.2.2 Ocular examination data

- Determination of the best corrected visual acuity (BCVA)
- Slit-lamp examination and checking the fundus with the help of a handheld biconvex lens
- Watzke-test

- Tonometry with Goldmann applanation tonometer
- Indirect ophthalmoscopy
- OCT scan (after 2001, patients underwent this examination)

3.2.3 Concomitant pre-operative symptoms of the operated eyes

Visual acuity

Optic axial length

Refraction

1= <-6.0 Sphere

2= -3.0~-6.0 Sphere

3= 0~-3.0 Sphere

4= normal

5= 0~+3.0 Sphere

6= >+3.0 Sphere

Watzke test

0= negative 1= positive

Centrocecal scotoma

0= negative 1= positive

Vitreous haemorrhage pre-operative

0= no 1= yes

Retinoschisis

0= no 1= yes

Posterior staphyloma

0= no 1= yes

Retinal pigment epithelium atrophy (RPEA)

0= no 1= peripheral RPEA 2= central RPEA

Macular gliosis

0= no 1= gliosis 2= pre-retinal membrane

Central retinal vein occlusion

0= no 1= yes

Macular edema

0= no 1= yes

Drusen

0= no

1= Drusen outside the macula

2= Macular drusen

Macular retinal detachment

0= no 1= yes

Macular sub-retinal dropsy

0= no 1= yes

Macular pucker

0= no 1= yes

Status of lens

0= No cataracts

1= Mild cataracts

2= Moderate cataracts

3= Severe cataracts

4= Pseudophakic eyes

5= Aphakic eyes

Vitreoretinal traction

0= no 1= yes

Deck of MH

0= no 1= yes

Peripheral retinal hole

0= no 1= yes

Quantity of peripheral retinal hole

Position of peripheral retinal hole

Area of retinal detachment

3.2.4 Operation details of MH

All the patients underwent PPV to treat MH, and the surgical procedure was recorded as follows:

ILM peeling

0= None

1= ILM peeling

2= Membrane ectomy

Dye

0= None

1= ICG, diluted 1: 5

2= ICG, diluted 1:4

3= ICG, diluted 1:3

4= ICG, diluted1:2

5= ICG, normal concentration

6= TA

7= BBG

Agglutination

0= None

1= Autologous thrombocytes

2= Autologous whole blood

3= Autologous serum

Intravitreal tamponade

0= None

1= Air

2= 20% SF6

3= 25% SF6

4= 30% SF6

5= 35% SF6

6= 40% SF6

7= Silicone oil

Endocryoretinopexy

0= no 1= yes

Exocryoretinopexy

0= no 1= yes

Retinectomy

0= no 1= yes

Endolaserphotocoagulation

0= no 1= yes

Iridectomy

0= no 1= yes

Encircling

0= no 1= yes

Perfluorodecalin

0= no 1= yes

3.2.5 Complications of MH surgery (intra- and post-operative)

Iatrogenic retinal hole (peripheral)

0= no 1= yes

Iatrogenic retinal hole (during peeling)

0= no 1= yes

Len touch during surgery

0= none

1= Mild, no need for treatment

2= Severe, cataract surgery must be performed

ILM rest after peeling

0= no ILM rest

1= ILM rest

2= no peeling

Retinal haemorrhage

0= no 1= yes

Hyphema post-operative

0= no 1= yes

Vitreous hemorrhage post-operatively

0= no 1= yes

Sub-retinal haemorrhage post-operatively

0= no 1= yes

Ocular hypertension

0= no 1 $\leq$ 30mmHg 2 $\geq$30mmHg

Cataract

0= no 1= yes 2= Pseudophakia

Dislocation of IOL

0= no 1= yes

Retinal detachment

0= no 1= yes

Peripheral retinal hole

0= no 1= yes

Infection

0= no 1= yes

Proliferative vitreous retinopathy (PVR)

0= no 1= yes

Macular gliosis

0= no 1= yes

Macular pucker

0= no 1= yes

Aftercataract

0= no 1= yes

Fibrin exudation

0= no 1= yes

Silicone oil prolapse

0= no 1= yes

Gas prolapse

0= no 1= yes

Secondary glaucoma

0= no 1= yes

Visual field defect

0= no 1= yes

Macular neovasculation

0= no 1= yes

Uveitis

0= no 1= yes

3.2.6 History of other surgeries in operated eyes

The histories of other surgical operations and treatments included the cause of the disease(s), dates of treatment, kinds of treatment (laserphotocoagulation [extent and location], cataract surgery [before and combined with or after first/second/third MH surgery], method used [phaco-emulsification and intraocular lens implantation {Phaco+IOL}, Phaco, lensectomy, or intracapsular cataract extraction {ICCE}], YAG laser treatment for after-cataract, retinal detachment surgery [size, shape, number, and position of retinal breaks], methods used [PPV, encircling band, local buckle, endo-, exocryoretinopexy, endolaser-photocoagulation, endodiathermy, perfluorodecalin, and kinds of intravitreal tamponade]), and other surgical operations.

3.2.7 Final assessment visit

Complaint of metamorphopsia

1= worse than before

2= better immediately after surgery, then getting worse

3= no change

4= better

5= clearly better

6= normal

Complaint o f centrocecal scotoma

1= worse than before

2= no change

3= better

4= clearly better

5= positive after surgery

BCVA (pre- and post-operative at last visit)

Intra-ocular pressure (IOP)

Status of lens

0= no cataract

1= mild cataract

2= moderate cataract

3= severe cataract

4= pseudophakic eye

5= aphakic eye

Location of IOL

0= normal lens

1= in capsule sack

2= in sulcus

3= fixed on sclera

After-cataract

0= none 1= mild 2= moderate 3= severe

Status of MH

0= close 1= never close 2= open again

Macular pigment epithelium (PE) defect

0= no 1= yes

Macular PE proliferation

0= no 1= yes

Pale optic disc

0= no 1= yes

Amsler grid

1= worse than before

2= better immediately after surgery, then getting worse

3= no change

4= better

5= clearly better

6= normal

Watzke test

0= negative 1= positive

We recorded changes in VA, including BCVA, pre-operatively, 1 month, 3months, 6months, 1 year, and 2 years after surgery and at the last visit, and documented the BCVAs as VA pre-operative, BCVA post-operative and final VA. Distance VA was measured with a Snellen VA chart. For purposes of statistical analysis, VA was recorded as sequence scores (Table2).

Table 2. Distance visual acuity was recorded in sequence score

Distance VA	Score
1.0	26
0.9	25
0.8	24
0.7	23
0.63	22
0.6	21
0.5	20
0.4	19
0.32	18
0.3	17
0.25	16
0.2	15
0.15	14
0.125	13
0.1	12
0.08	11
0.06	10
0.05 1/20	9
0.04 1/25	8
0.03 1/35	7
0.02 1/50	6
0.015 1/65	5
count finger	4
hand movement	3
light perception	2
light perception defect	1
no light perception	0

3.3 Statistical analysis

SPSS software 15.0 (SPSS Inc., Chicago, IL, USA) were used to perform statistical analyses. Descriptive statistics are given as the mean and standard deviation, median, and range for continuous data. To calculate the statistical univariate and multivariate analyses, we used Pearson chi-square, Fisher two-tail exact test, Wilcoxon signed rank test, Npar tests, Kruskal-Wallis test, and stepwise logistic regression test. A ***P*** value ≤0.05 was considered to be significant.

4. Results

4.1 General clinical data

Four hundred fifty-one patients involving 487 eyes were enrolled, including 123 (27.3%) males and 328 (72.7%) females, with an average age of 64.92±9.48 years and a mean follow-up of 43.10±37.35 months (range, 3-163 months). Of 451 patients, 96 (21.3%) had bilateral lesions, including 24 (25.0%) males and 72 (75.0%) females. Thirty-six patients underwent bilateral MH surgery in our hospital, including 9 males and 27 females, and 60 patients underwent unilateral surgery in our hospital, including 15 males and 45 females. After initial surgery, the success rate was 89.7% (437 eyes), with 8 eyes requiring no further surgery. Forty-two eyes underwent a second surgery, with a success rate of 88.1% (37 eyes). Four eyes had a third surgery, and 75.0% (3 eyes) achieved anatomic closure of the MH. The MH was closed in 477 (97.9%) eyes after one or more surgeries, while 3 (0.6%) eyes remained open and 7 (1.4%) eyes re-opened after a period of time following surgery.

According to the pathogenesis of MHs, the cases were divided into four groups (idiopathic, highly myopia, traumatic, and secondary MH) and the statistical analysis was conducted according to the four groups.

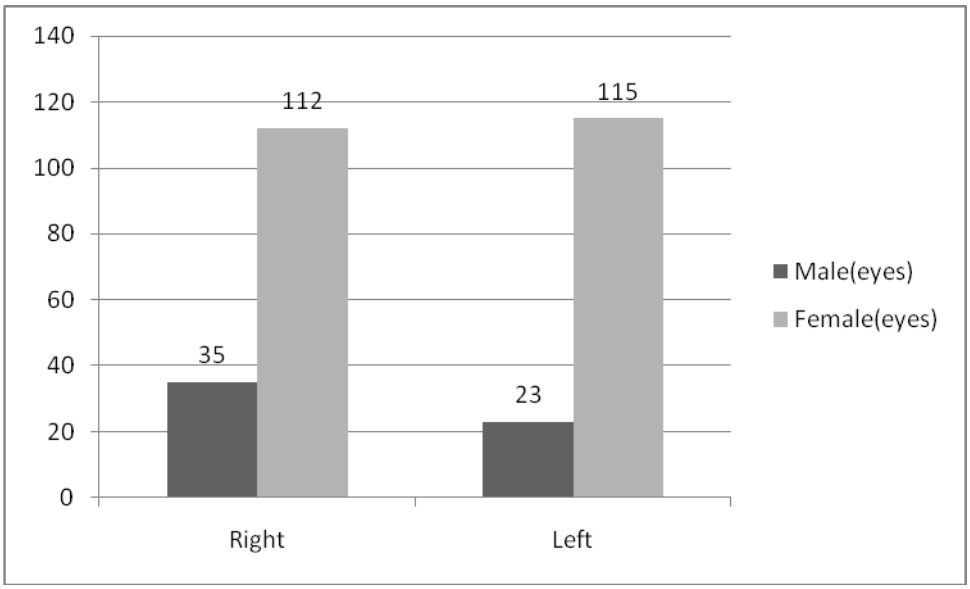
4.2 IMH group

4.2.1 General clinical data of IMH

Two hundred eighty-five eyes of 264 patients were included. Among the patients, 55 were males (20.8%) and 209 were females (79.2%), with an average age of 66.29±7.02 years (range, 32.5~84 years) and a mean follow-up of 43.07±38.70 months (range, 3~161 months). Of 264 patients, 60 (22.7%) had bilateral lesions, including 10 (16.7%) males and 50 (83.3%) females. Among the patients, 21 underwent bilateral MH surgery in our hospital, including 3 males and 18 females. Thirty-nine patients underwent unilateral surgery in our hospital, including 7 males and 32 females. Among the patients who had unilateral lesions, 45 were males (22.1%) and 159 were females (77.9%).

The incidence of unilateral or bilateral lesions showed no gender difference as confirmed by Pearson's chi-square test (Pearson's $\chi 2 = 1.292$, $P = 0.256 > 0.05$). The age of unilateral MH patients was 66.59±7.37 years (range, 32.5-84 years). The patients with bilateral lesions underwent initial MH surgery at 65.56±6.03 years of age (range, 49-76 years). An independent samples t-test with Levene's test for equality of variances was used for comparison of age differences between patients with unilateral and bilateral lesions and showed that two subsets of patients were derived from the population of same age ($F=1.133$, $P = 0.288 > 0.05$), thus, it was considered that the incidence of unilateral or bilateral lesions showed no significant age difference ($t=1.123$, $P=2.263 > 0.05$), suggesting that MH prevailed among the elderly population. The binomial non-parametric test (Npar test) showed that the incidence of MH in patients with either single or bilateral lesions was significantly higher in females than males ($P = 0.000 < 0.05$); however, the incidence of right or left MH showed no gender difference, as confirmed by Pearson's chi-square test ($\chi 2 = 2.240$, $P = 0.134 > 0.05$; Fig.15).

Fig. 15 Incidence of IMH



4.2.2 Stadium of IMH

Table 3 Stadium in every MH operation

Stadium	1st MH OP	2nd MH OP	3rd MH OP
I	2		
II	33		
III	139	7	
IV	111	22	3
Total	285	29	3

Binary logistic regression showed that the initial MH stadium has no significant connection with the initial result of the surgery (P = 0.1683 >0.05).

4.2.3 Course of IMH

Table 4-1 Course of IMH

Course	Frequency			Percent	Cumulative Percent
	Unilateral	Bilateral	Total		
1 (<1week)	7	5	12	4.2	4.2
2 (<1month)	53	18	71	24.9	29.1
3 (1～3months)	50	13	63	22.1	51.2
4 (3～6months)	33	18	51	17.9	69.1
5 (6～12months)	34	18	52	18.3	87.4
6 (12～36months)	27	9	36	12.6	100.0
Total	204	81	285	100.0	100.0

Table4-2 Relationship between initial success rate and IMH course

Case	Course of IMH						Total	Logistic Regression
	1	2	3	4	5	6		
Succeed	10	65	55	42	49	30	251	
Fail	2	6	8	9	3	6	34	P=0.7103
Total	12	71	63	51	52	36	285	

Binary logistic regression showed that the history of IMH was not significantly associated with the success rate of MH surgery (P = 0.7103 >0.05).

4.2.4 Success rate of IMH surgery

After initial surgery, the success rate was 88.1% (251 eyes), with 5 eyes requiring no further surgery. Twenty-nine eyes underwent a second surgery, with a success rate of 86.2% (25 eyes). Three eyes had a third surgery, and 66.6% (2 eyes) achieved anatomic closure of the MH. The MH was closed in 278 (97.5%) eyes after one or more operations, while 3 (1.1%) eyes remained open and 4 (1.4%) eyes re-opened after a period of time following operation.

4.2.5 Refraction and optic axial length of the operated eye in IMH group

The average optic axial length of the patients in this group was 23.14±1.01mm, (range 19.79~25.78mm).

Refraction	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1 = <-6.0 Sphere	2	0.7	2	0.7
2 = -3.0~-6.0 Sphere	27	9.5	29	10.2
3 = 0~-3.0 Sphere	52	18.2	81	28.4
4 = normal	31	10.9	112	39.3
5 = 0~+3.0 Sphere	152	53.3	264	92.6
6 = >+3.0 Sphere	19	6.7	283	99.3
7 = unclear	2	0.7	285	100.0

4.2.6 Relationship between cataract and IMH surgeries

	Case	Percent
No cataract surgery	51	17.9%
With 1st MH-OP	51	17.9%
Before 2nd MH-OP	167	58.6%
With 2nd MH-OP	7	2.5%
Before 3rd MH-OP	9	3.1%
Total	285	100%

4.2.7 Surgical details of IMH-OP

	1st OP	2nd OP	3rd OP
	(case/percent)	(case/percent)	(case/percent)
ILM peeling			
None	42/285(14.7%)	12/29(41.4%)	1/3(66.7%)
ILM peeling	243/285(85.3%)	17/29(58.6%)	2/3(33.3%)
Dye			
None	110/285(38.6%)	9/29(31.0%)	1/3(33.3%)
ICG, normal concentration	110/285(38.6%)	17/29(58.6%)	2/3(66.7%)
ICG, diluted 1:4	2/285(0.7%)	0	0
ICG, diluted 1: 5	62/285(21.8%)	3/29(10.3%)	0
BBG	1/285(0.4%)	0	0
Agglutination			
None	9/285(3.2%)	0	0
Autologous thrombocytes	272/285(95.4%)	28/29(96.6%)	3/3(100%)
Autologous whole blood	4/285(1.4%)	1/29(3.4%)	0
Intravitreal tamponade			
None	1/285(0.4%)	0	0
40%SF6	1/285(0.4%)	0	0
35% SF6	2/285(0.7%)	0	0
30% SF6	64/285(22.5%)	9/29(31.0%)	2/3(66.7%)
25% SF6	210/285(73.7%)	19/29(65.5%)	0
20%SF6	6/285(2.1%)	1/29(3.5%)	0
Air	1/285(0.4%)	0	0
Silicone oil	0	0	1/3(33.3%)
Perfluorodecalin	1/285(0.4%)	1/29(3.5%)	1/3(33.3%)

The MH was closed in 251 eyes and not closed in 34 eyes after first operation. Among the failed cases, 13 eyes had residual ILM and 8 eyes did not undergo ILM

peeling.

Eleven eyes with residual ILM and 6 eyes without ILM peeling in the first surgery underwent ILM peeling in the second surgery. Among the 17 eyes, 1eye had macular pucker and 7 eyes had ERM in the macular region. The MH was successfully closed in 15 eyes and not closed in 2 eyes after surgery. All these eyes had ILM rest and 1 eye had RRD after surgery. Among the 12 eyes without ILM peeling in the second surgery, the MH was successfully closed in 10 eyes and not closed in 2 eyes. Among the failed cases, 1 eye had ILM rest shown by ICG staining, but failed to carry out complete ILM peeling, and the MH was expanded after surgery. The patient declined the third surgical treatment.

Among the 3 eyes undergoing the third surgery, 1 eye had no residual ILM confirmed by ICG staining due to macular edema and did not undergo ILM peeling. The other 2 eyes underwent ILM peeling again. Among the 2 eyes, 1 eye had ILM rest after ILM peeling twice without the assistance of staining and showed no ILM rest after the third ILM peeling under ICG intervention. ERM was formed in the macular region after surgery and the third surgery failed. The other eye had ILM rest after the first ILM peeling without the assistance of staining, and still had ILM rest after the second ILM peeling with the assistance of ICG. RRD developed and MH relapsed after surgery. The eye had the third ILM peeling without the assistance of staining and the MH was closed.

4.2.8 Correlation between intra-operative ILM peeling, post-operative ILM rest and ERM of the IMH group

Fig. 16 Correlation between ILM peeling and post-operative macular ERM

Continuity corrected chi-square=1.281, P=0.258

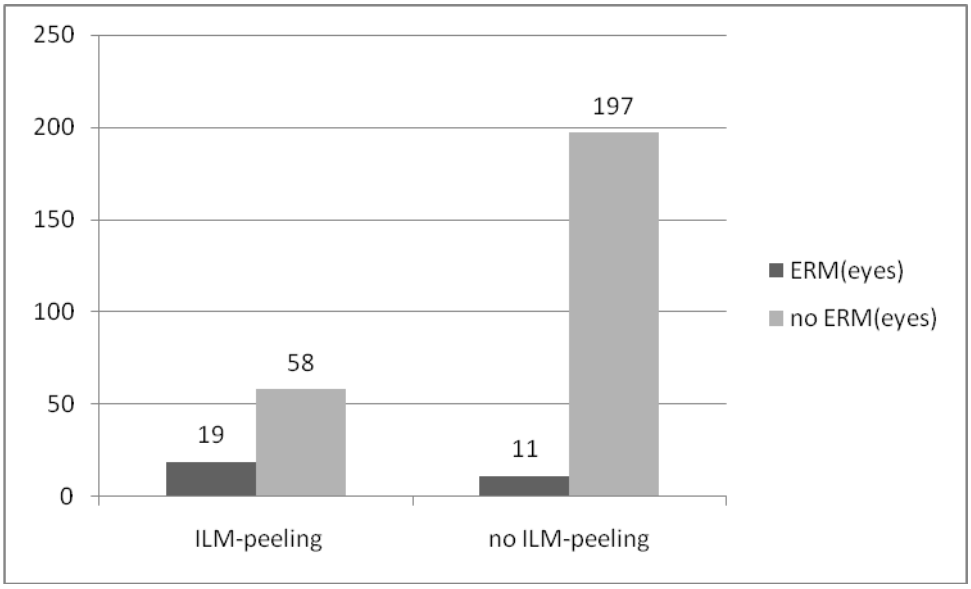


Fig.17.Correlation between ILM rest (including whole ILM rest) and no ILM rest and intra-operative macular ERM

Pearson chi-square=22.426, P=0.000

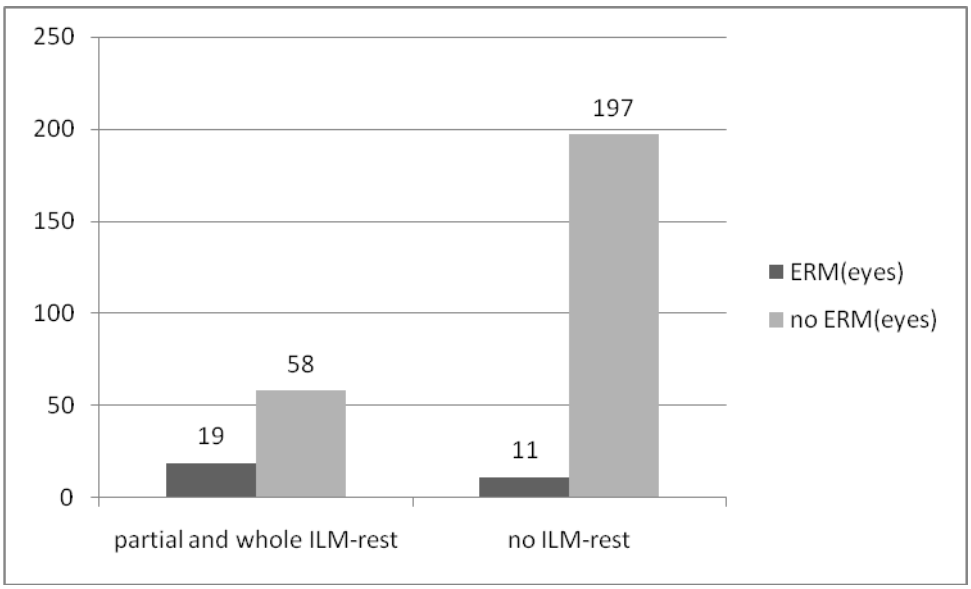


Fig. 18.Correlation between ILM rest, no ILM rest, and post-operative ERM

Continuity corrected chi-square=26.11, P=0.000

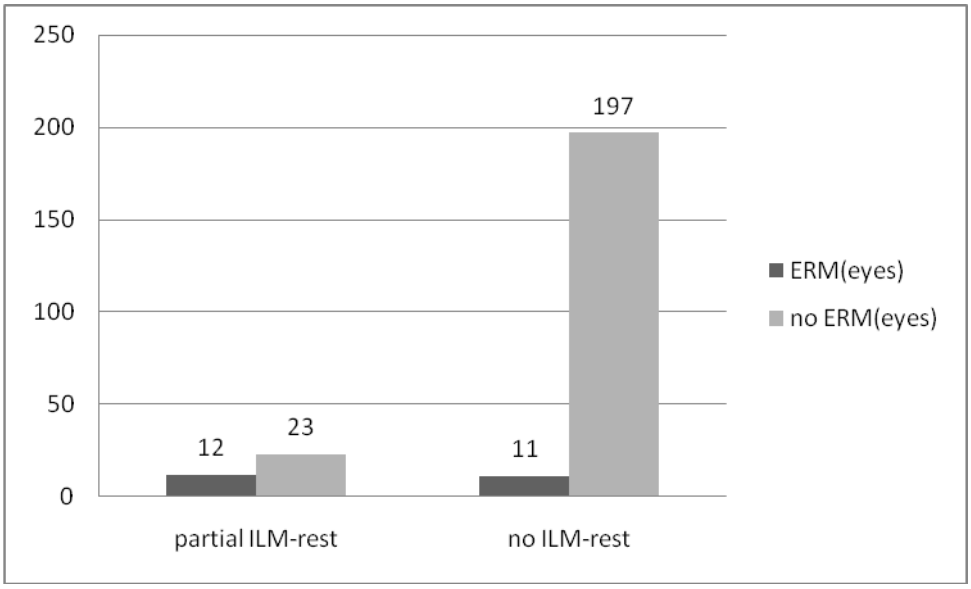
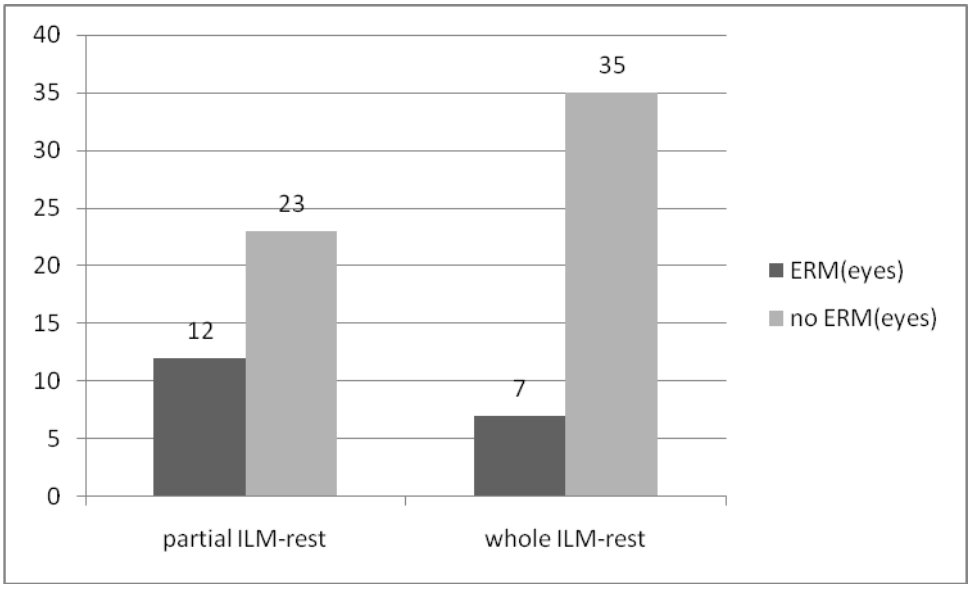


Fig. 19. Correlation between partial or whole ILM rest and post-operative ERM

Pearson chi-square=3.189, P=0.074



4.2.9 Complications of IMH surgery (intra- and post-operative)

	1st OP	**2nd OP**	**3rd OP**
	(case/percent)	(case/percent)	(case/percent)
Iatrogenic retinal hole (peripheral)	12/285(4.2%)	2/29(7.1%)	0
Iatrogenic retinal hole (during peeling)	0	0	0
Lens touch during surgery			
Mild, no need to handle	1/285(0.4%)	0	0
Severe, cataract surgery necessary	0	0	0
Cataract	216/285(76.3%)	11/29(37.9%)	0
ILM rest after peeling	35/285(12.3%)	3/29(10.3%)	0
All ILM remain (without peeling)	42/285(14.7)	4/29(13.8%)	0
Retinal haemorrhage	16/285(5.6%)	2/29(6.9%)	0
Hyphema, post-operative	2/285(0.7%)	0	0
Vitreous haemorrhage, post-operatively	13/285 (4.6%)	2/29(6.9%)	0
Ocular hypertension			
None	37/285(13.0%)	4/29(13.8%)	1/3(33.3%)
<30mmHg	88/285(30.9%)	16/29(55.2%)	2/3(66.7%)
>30mmHg	160/285(56.1%)	9/29(31.0%)	0
RD	19/285(6.7%)	3/29(10.3%)	0
Peripheral retinal hole			
New hole	23/285(8.1%)	2/29(6.9%)	0
Infection	2/285(0.7%)	0	0
PVR	4/285(1.4%)	0	0
Macular ERM	30/285(10.5%)	3/29(10.3%)	1/3(33.3%)
Macular pucker	2/285(0.7%)	0	0

Aftercataract	7/285(2.5%)	4/29(13.8%)	0
Fibrin exudation	5/285(1.8%)	1/29(3.4%)	0
Gas prolapse	1/285(0.4%)	0	0
Secondary glaucoma	8/285(2.8%)	0	0
Visual field defect	4/285(1.4%)	2/29(6.9%)	0
Choroidal detachment	2/285(1.5%)	0	0
Fistula of corneoscleral tunnel	1/285(0.4%)	0	0

Table 5 Relationship between visual field defect and possible related factors

	Visual field defect (case)	No visual field defect (case)	Chi-square	P
With dye	3	172	0.002*	0.964
Without dye	1	109		
Pigment proliferation	2	108	0.000*	1.0
No pigment proliferation	2	173		
Pigment defect	0	33	---#	1.0
No pigment defect	4	248		
Optic disc paleness	0	38	---#	1.0
No optic disc paleness	4	243		
Post-operative secondary glaucoma	0	8	---#	1.0
No post-operative secondary glaucoma	4	273		

*Continuity corrected chi-square; #Fisher's exact test

4.2.10 History of other surgeries in the eyes of IMH

One hundred six (106) eyes (37.2%) underwent only MH-OP, while the remainder had other intra-ocular surgeries in addition to MH-OP. One hundred thirty-two eyes had 1 (46.3%), 35 eyes had 2 (12.3%), 10 eyes had 3 (3.5%), 1 eye had 4 (0.35%), and 1 eye had 5 other intra-ocular surgeries (0.35%).

Table 6-1 After first MH-OP

Diagnosis	Eyes undergoing surgery after 1st IMH-OP				
	1st	2nd	3rd	4th	5th
Cataract	143	10	2		
RRD	16	1			
RD	1				
Rhegmatogenous retinal redetachment		3	1	2	
Silicon oil removal		1	1		1
Aftercataract	2	23	5		
IOL dislocation		3			
Iriscapture		1	1		
Ocular tension decompensation	1				
Endophthalmitis	2				
Occlusion of pupil		1			
Vitreous hemorrhage	2				
RD with pseudophakia	1	1			
Fistula of corneoscleral tunnel	1				
Total	169	44	10	5	2

Table 6-2 After 2nd IMH-OP

Diagnosis	Eyes undergoing surgery after 2nd IMH-OP		
	1st	2nd	3rd
Cataract	9		
RD	1	1	
Secondary glaucoma	1		
Silicon emulsification	1		
Aftercataract		2	
IOL dislocation		1	1
Total	12	4	1

Table 6-3 After 3rd IMH-OP

Diagnosis	Eyes undergoing surgery after 3rdIMH-OP		
	1st	2nd	3rd
IOL dislocation	1		
Total	1	0	0

4.2.11 Visual outcomes of IMH surgery

Distance vision

	Pre-operative	Best VA post-operatively	Final VA
<0.1	41 (14.4%)	14 (4.9%)	28 (9.8%)
0.1~0.4	202 (70.9%)	97 (34.0%)	101 (35.5%)
≥0.4	42 (14.7%)	174 (61.1%)	156 (54.7%)

Distance Visual outcome

	BCVA pre-operatively	Final VA pre-operatively	Final VA-BCVA
Improved	228 (80.0%)	205 (71.9%)	----
Stable	24 (8.4%)	25 (8.8%)	190 (66.7%)
Worsened	33 (11.6%)	55 (19.3%)	95 (33.3%)
P Value	0.000	0.000	0.000
t	15.52	10.038	-8.633

Post-operatively, 228 (80.0%) and 205 (71.9%) eyes had improvement in distance visual on one visit and the final visit, respectively**.** Visual acuity ≥0.4 was achieved in 174 (61.1%) and 156 (54.7%) eyes on one and the final post-operative visit, while 28 (9.8%) eyes had a VA< 0.1. The post-operative final VA improved in 205 (71.9%) eyes, remained stable in 25 eyes (8.8%), and worsened in 55 eyes (19.3%). The post-operative BCVA and final VA were both significantly better than the pre-operative values (P=0.000); however, compared with BCVA, 95 eyes had worse VA on the final visit. The final VA exhibited a significant decline in trend compared with BCVA (P=0.000).

The correlation between IMH stage and the pre-operative VA, post-operative BCVA, and post-operative final VA was tested using Spearman's rho test, which showed no statistical significance between IMH stage and the pre-operative VA, post-operative BCVA, and post-operative final VA (P=0.144, P=0.156, and P=0.312, respectively). After deduction, the influence of pre-operative cataract opacification on the pre-operative VA, a partial correlation test showed that with increasing MH stage, the pre-operative VA decreased (r=-0.522, P=0.000). After deduction of cataract opacification during the post-operative follow-up on post-operative final VA, no statistical significance between MH stage and post-operative final VA was noted (P=0.484).

4.2.12 Analysis of factors influencing IMH surgery results

In the current study the MH surgery results were assessed in two ways, as follows: whether or not the MH was closed; and the post-operative VA recovery, including the changes in post-operative BCVA and pre-operative VA, the changes in post-operative final VA and pre-operative VA, as well as the changes in post-operative final VA and post-operative BCVA. The MH surgery results are influenced by multiple factors, including pre-, intra-, and post-operative parameters. Based on the different categories of influencing and outcome variables, the corresponding statistical tests were carried out, including the continuity corrected chi-square test, Pearson chi-square test, Wilcoxon signed rank test, Kruskal-Wallis test, Spearman's rho test, and logistic regression. The influencing factors included pre-operative concomitant symptoms, surgical details, post-operative complications, as well as stadium, and course of disease.

4.2.12.1 Analysis of factors influencing post-operative anatomic repair in IMH surgery

Table 7-1 Analysis of factors influencing the success of the first IMH surgery

	Statistical method	Chi-square	P	OR
ILM peeling	Pearson chi-square	2.375	0.123	
Staining	Pearson chi-square	2.588	0.108	
ILM rest	Pearson chi-square	29.588	0.000	
Cataract surgery	Continuity corrected chi-square	0.65	0.420	
ICG staining	Fisher's exact test		1.000	
Gas tamponade	Fisher's exact test		1.000	
Agglutination	Fisher's exact test		1.000	
Different agglutinations	Fisher's exact test		0.006	

RD after initial MH-OP	Fisher's exact test		1.000	
ICG staining at different concentrations	Logistic regression		0.321	1.167
Gas tamponade at different concentrations	Logistic regression		0.213	0.622
MH stage	Logistic regression		0.168	1.483
Course of disease	Logistic regression		0.710	1.048
Pre-operative VA	Logistic regression		0.000	1.35
Optic axial length	Logistic regression		0.289	0.819
Refraction	Logistic regression		0.755	0.954
Number of intra-ocular surgeries after initial MH-OP	Logistic regression		0.000	7.606
Total number of MH-OP	Logistic Regression		0.932	999.0
Total number of intra-ocular surgeries	Logistic regression		0.259	0.757

Table 7-2 Analysis of factors influencing final closure in IMH

	Statistical method	Chi-square	P	OR
ILM peeling	Fisher's exact test		1.000	
Staining	Fisher's exact test		0.676	
ICG Staining	Fisher's exact test		1.000	
Gas tamponade	Fisher's exact test		1.000	
Agglutination	Fisher's exact test		1.000	
Different agglutinations	Fisher's exact test		1.000	
Cataract surgery	Fisher's exact test		0.615	
RD after initial MH-OP	Fisher's exact test		1.000	
ILM rest	Fisher's exact test	5.284	0.040	

ICG staining at different concentrations	Logistic regression	0.403	1.211
Gas tamponade at different concentrations	Logistic regression	0.683	1.375
MH stage	Logistic regression	0.091	0.267
Course of disease	Logistic regression	0.974	1.009
Pre-operative VA	Logistic regression	0.008	1.509
Optic axial length	Logistic regression	0.554	0.799
Refraction	Logistic regression	0.212	0.596
Number of intra-ocular surgeries after initial MH-OP	Logistic regression	0.055	7.442
Total number of MH-OP	Logistic regression	0.303	0.261
Total number of intra-ocular surgeries	Logistic regression	0.177	2.385

4.2.12.2 Analysis of factors influencing post-operative visual acuity recovery after IMH surgery

Table 8-1 Analysis of factors influencing post-operative BCVA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test	7.118		0.018	
ILM rest	Fisher's exact test	2.983		0.555	
Pigment epithelial atrophy	Kruskal-Wallis test	5.777		0.056	
Fundus hemorrhage	Kruskal-Wallis test	0.102		0.951	

ICG staining at different concentrations	Spearman's rho		0.199	0.098
Gas tamponade at different concentrations	Spearman's rho		0.161	0.083
MH stage	Spearman's rho		0.879	0.009
Course of disease	Spearman's rho		0.673	-0.025
Pre-operative VA	Spearman's rho		0.007	-0.159
Optic axial length	Spearman's rho		0.915	0.007
Refraction	Spearman's rho		0.481	-0.042
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho		0.002	0.180
Total number of MH-OP	Spearman's rho		0.308	-0.061
Total number of intra-ocular surgeries	Spearman's rho		0.011	0.152
Cataract degree (final follow-up)	Spearman's rho		0.000	-0.306
Centrocecal scotoma	Spearman's rho		0.000	-0.299
Amsler grid	Spearman's rho		0.000	-0.343
ILM peeling	Wilcoxon signed rank test	-0.064	0.949	
Staining	Wilcoxon signed rank test	0.848	0.396	
ICG staining	Wilcoxon signed rank test	0.504	0.614	
Gas tamponade	Wilcoxon signed rank test	0.488	0.625	
Agglutination	Wilcoxon signed rank test	0.024	0.981	
Different agglutinations	Wilcoxon signed rank test	-1.451	0.147	
Cataract surgery	Wilcoxon signed rank test	-4.692	0.000	
Macular edema	Wilcoxon signed rank test	0.692	0.489	

Pigmentation	Wilcoxon signed rank test	-0.722	0.470	
Optic disc paleness	Wilcoxon signed rank test	-1.558	0.119	
Secondary glaucoma	Wilcoxon signed rank test	-1.455	0.146	
Visual field defect	Wilcoxon signed rank test	-4.146	0.000	

Table 8-2 Analysis of factors influencing post-operative final visual acuity improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test	6.791		0.030	
ILM rest	Fisher's exact test	4.540		0.332	
Pigment epithelial atrophy	Kruskal-Wallis test	9.864		0.007	
Fundus hemorrhage	Kruskal-Wallis test	2.067		0.356	
ICG staining at different concentrations	Spearman's rho			0.402	0.064
Gas tamponade at different concentrations	Spearman's rho			0.742	0.020
MH stage	Spearman's rho			0.678	0.025
Course of disease	Spearman's rho			0.831	-0.013
Pre-operative VA	Spearman's rho			0.034	-0.126
Optic axial length	Spearman's rho			0.288	-0.066
Refraction	Spearman's rho			0.704	-0.023
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho			0.049	0.117
Total number of MH-OP	Spearman's rho			0.056	-0.113

Total number of intra-ocular surgeries	Spearman's rho		0.076	0.106
Cataract degree (final follow-up)	Spearman's rho		0.000	-0.237
Centrocecal scotoma	Spearman's rho		0.000	-0.351
Amsler grid	Spearman's rho		0.000	-0.305
ILM peeling	Wilcoxon signed rank test	-0.951	0.341	
Staining	Wilcoxon signed rank test	-1.137	0.256	
ICG staining	Wilcoxon signed rank test	0.565	0.572	
Gas tamponade	Wilcoxon signed rank test	-1.768	0.077	
Agglutination	Wilcoxon signed rank test	-1.355	0.176	
Different agglutinations	Wilcoxon signed rank test	-1.197	0.231	
Cataract surgery	Wilcoxon signed rank test	-3.485	0.001	
Macular edema	Wilcoxon signed rank test	0.867	0.386	
Pigmentation	Wilcoxon signed rank test	-1.255	0.209	
Optic disc paleness	Wilcoxon signed rank test	-2.300	0.022	
Secondary glaucoma	Wilcoxon signed rank test	-1.641	0.101	
Visual field defect	Wilcoxon signed rank test	-3.551	0.000	

Table 8-3 Analysis of factors influencing post-operative final visual acuity impairment in comparison with BCVA

	Statistical method	Chi-square	P	OR
ILM peeling	Pearson Chi-square	10.179	0.001	
Staining	Pearson Chi-square	10.129	0.001	
Cataract surgery	Pearson Chi-square	1.988	0.159	
ILM rest	Pearson Chi-square	13.398	0.001	
Pigment epithelial atrophy	Pearson Chi-square	11.889	0.003	
Optic disc paleness	Pearson Chi-square	3.611	0.057	

Fundus hemorrhage	Pearson Chi-square	1.387	0.500	
Agglutination	Continuity corrected Chi-square	1.162	0.281	
Pigmentation	Continuity corrected Chi-square	16.415	0.001	
Secondary glaucoma	Continuity corrected Chi-square	0.000	1.000	
ICG staining	Fisher's exact test		1.000	
Gas tamponade	Fisher's exact test		0.333	
Different agglutinations	Fisher's exact test		0.599	
RD after initial MH-OP	Fisher's exact test	2.082	0.149	
Macular edema	Fisher's exact test		1.000	
Visual field defect	Fisher's exact test		0.604	
ICG staining at different concentrations	Logistic regression		0.004	0.717
Gas tamponade at different concentrations	Logistic regression		0.447	1.200
MH stage	Logistic regression		0.668	1.083
Course of disease	Logistic regression		1.000	1.000
Pre-operative VA	Logistic regression		0.460	1.030
Optic axial length	Logistic regression		0.288	-0.066
Refraction	Logistic regression		0.091	0.837
Number of intra-ocular surgeries after initial MH-OP	Logistic regression		0.140	1.248
Total number of MH-OP	Logistic regression		0.005	0.358
Total number of intra-ocular surgeries	Logistic regression		0.098	1.279
Cataract degree (final	Logistic regression		0.182	0.618

follow-up)			
Centrocecal scotoma	Logistic regression	0.002	0.632
Amsler grid	Logistic regression	0.002	0.659

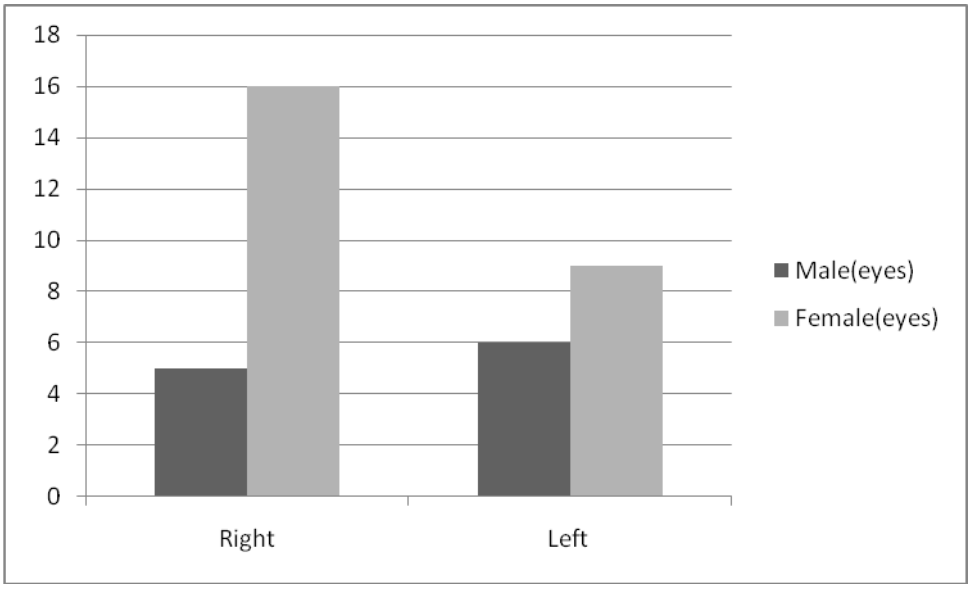
4.3 HMMH group

4.3.1 General clinical data of HMMH

Thirty-six eyes of 33 patients were included. Among the 33 patients, 10 were males (30.3%) and 23 were females (69.7%), with an average age of 60.19±9.05 years (range, 41.0~85 years) and a mean follow-up of 54.21±36.45 months (range, 5.5~126.0 months). Of 33 patients, 7 (21.2%) had bilateral lesions, including 3 (42.9%) males and 4 (57.1%) females. Among the 33 patients, 3 underwent bilateral MH surgery in our hospital, including 1 male and 2 females, and 30 underwent unilateral surgery in our hospital, including 9 males and 21 females. Among the patients who had unilateral lesions, 7 were males (26.9%) and 19 were females (73.1%).

The incidence of unilateral or bilateral lesions showed no gender differences, as confirmed by Pearson's chi-square test (Pearson's χ^2 = 0.123, *P* = 0.726 >0.05). The age of unilateral MH patients was 60.60±7.40 years (range, 50.0-75.0 years). The patients with bilateral lesions underwent initial MH surgery as part of the current research at the age of 59.15±12.82 years (range, 41.0-85.0 years). An independent samples t-test with Levene's test for equality of variances for the comparison of the age difference between patients with unilateral and bilateral lesions showed 2 subsets of patients derived from the population of the same age (F=1.932, *P* = 0.174 >0.05). The incidence of unilateral or bilateral lesions showed no significant age difference (t=0.425, P=0.674 >0.05), suggesting that HMMH also prevailed among the elderly population. The binomial non-parametric test (Npar test) showed that the incidence of MH in patients with single or bilateral lesions was significantly higher in females than males (*P* = 0.029 <0.05); however, the incidence of right or left MH showed no gender difference as confirmed by Pearson's chi-square test (χ^2 =0.453, *P* = 0.501 >0.05; Fig. 20).

Fig. 20 Incidence of HMMH.



4.3.2 Stadium of HMMH

Table 9 Stadium in every HMMH operation

Stadium	1st MH OP	2nd MH OP	3rd MH OP
I			
II	5		
III	12		
IV	19	5	
Total	36	5	0

Binary logistic regression showed that the initial HMMH stadium had no significant connection with the initial result of the surgery (P = 0.9703 >0.05).

4.3.3 Course of HMMH

Table 10-1 Course of HMMH

Course	Frequency	Percent	Cumulative Percentage
1 (<1week)	12	33.3	33.3
2 (<1month)	6	16.7	50.0
3 (1～3months)	7	19.4	69.4
4 (3～6months)	2	5.6	75.0
5 (6～12months)	4	11.1	86.1
6 (12～36months)	5	13.9	100.0
Total	36	100.0	100.0

Table10-2 Relationship between initial success rate and HMMH course

Case	Course of IMH						Total	Logistic Regression
	1	2	3	4	5	6		
Succeed	11	5	6	2	2	5	31	
Fail	1	1	1	0	2	0	5	P=0.6511
Total	12	6	7	2	4	5	36	

Binary logistic regression showed that the history of HMMH was not significantly associated with the success rate of MH surgery (P = 0.6511 >0.05).

4.3.4 Success rate of HMMH surgery

After initial surgery, the success rate was 86.1% (31 eyes); 5 eyes underwent a second surgery, with a success rate of 100%. The MH was closed in all 36 (100.0%) eyes after one or two operations.

4.3.5 Refraction and optic axial length of operated eyes in the HMMH group

The average optic axial length of the patients in this group was 27.67±1.72mm, (range, 25.24~31.70mm). The refraction of all patients in this group was highly myopic (<-6.0 Sphere).

4.3.6 Relationship between cataract and HMMH surgeries

	Case	Percentage
No cataract surgery	4	11.1%
With 1st MH-OP	5	13.9%
Before 2nd MH-OP	23	63.9%
With 2nd MH-OP	4	11.1%
Before 3rd MH-OP	0	0
Total	36	100%

4.3.7 Surgical details of HMMH-OP

	1st OP (case/percent)	2nd OP (case/percent)
ILM peeling		
None	11/36(30.6%)	1/5(20.0%)
ILM peeling	25/36(69.4%)	4/5(80.0%)
Dye		
None	21/36(58.3%)	1/5(20.0%)
ICG, normal concentration	8/36(22.2%)	4/5(80.0%)
ICG, diluted 1: 5	6/36(16.7%)	0
TA	1/36(2.8%)	0
Agglutination		
None	5/36(13.9%)	1/5(20.0%)

Autologous thrombocytes	31/36(86.1%)	4/5(80.0%)
Intravitreal tamponade		
35% SF6	2/36(5.6%)	1/5(20.0%)
30% SF6	6/36(16.7%)	1/5(20.0%)
25% SF6	25/36(69.4%)	2/5(40.0%)
20%SF6	1/36(2.8%)	1/5(20.0%)
Silicone oil	2/36(5.6%)	0
Endocryoretinopexy		
Peripheral retinal hole	6/36(16.7%)	2/5(40.0%)
MH	1/36(2.8%)	0
Exocryoretinopexy	9/36(25.0%)	1/5(20.1%)

The MH was closed in 31 eyes and not closed in 5 eyes after the first surgery. Among the cases of failure, 2 eyes had residual ILM and 3 eyes did not undergo ILM peeling.

The 2 eyes with ILM rest underwent the second surgery for ILM peeling and the MH was successfully closed. Among the 3 eyes not undergoing ILM peeling during the first surgery, 1 eye did not undergo ILM peeling and 2 eyes underwent ILM peeling in the second surgery; however, 1 eye still had ILM rest. Finally, the surgery for all three eyes succeeded.

4.3.8 Complications of HMMH surgery (intra- and post-operative)

	1st OP	**2nd OP**
	(case/percent)	(case/percent)
Lens touch during surgery		
Mild, no need to handle	1/36(2.8%)	0
Cataract	30/36(83.3%)	0
ILM rest after peeling	6/36(16.7%)	1/5(20.0%)
ILM remain (without peeling)	11/36(30.6%)	1/5(20.0%)

Retinal hemorrhage	3/36(8.3%)	2/5(40%)
Vitreous hemorrhage, post-operatively	3/36 (8.3%)	1/5(20%)
Ocular hypertension		
None	3/36(8.3%)	1/5(20.0%)
<30mmHg	15/36(41.7%)	3/5(60.0%)
>30mmHg	18/36(50.0%)	1/5(20.0%)
RD	6/36(16.7%)	0
Peripheral retinal hole		
New hole	5/36(13.9%)	0
PVR	1/36(2.8%)	0
Macular ERM	1/36(2.8%)	0
Choroidal detachment	1/36(2.8%)	0

4.3.9 History of other surgeries in eyes of HMMH

Eleven (11) eyes (30.6%) underwent only MH-OP, while the remainder had other intra-ocular surgery or surgeries in addition to MH-OP. Eighteen eyes had 1 (50.0%), 4 eyes had 2 (11.1%), 2 eyes had 3 (5.6%), and 1 eye had 4intra-ocular surgeries (2.8%). During our observation period, patients who underwent asecond MH operation did not undergo further eye operations.

Table 11 After first HMMH-OP

Diagnosis	Eyes undergoing surgery after 1st HMMH-OP				
	1st	2nd	3rd	4th	5th
Cataract	19	2	1		
RRD	2				
RD	1				
Rhegmatogenous retinal	1	1	1		

re-detachment					
Silicon oil removal	1			1	
Aftercataract		3	1		
IOL dislocation	1				
Iriscapture		1	1		
Total	25	7	3	1	

4.3.10 Visual outcomes of HMMH surgery

Distance vision

	Pre-operative	Best VA post-operatively	Final VA
<0.1	14 (38.9%)	8 (22.2%)	11 (30.5%)
0.1~0.4	16 (44.4%)	5 (13.9%)	6 (16.7%)
≥0.4	6 (16.7%)	23 (63.9%)	19 (52.8%)

Distance visual outcome

	BCVA pre-operatively	Final VA pre-operatively	Final VA-BCVA
Improved	30 (83.4%)	27 (75.0%)	----
Stable	3 (8.3%)	1 (2.8%)	25 (69.4%)
Worsened	3 (8.3%)	8 (22.2%)	11 (30.6%)
P Value	0.000	0.000	0.014
t	6.582	4.418	-2.586

Post-operatively, 30 (83.4%) and 27 (75.0%) eyes had improved distance vision on one visit and the final visit, respectively**.** Visual acuity ≥0.4 was achieved in 23 (63.9%) and 19 (52.8%) eyes on one and the final post-operative visit, while 11 (30.5%) eyes had <0.1. Post-operative final VA improved in 27 (75.0%) eyes, remained stable in 1 (2.8%) and worsened in 8 eyes (22.2%). Post-operative BCVA and final VA were

significantly better than pre-operative (P=0.000) values; however, compared with BCVA, 11 eyes had a worse VA on the final visit and the final VA significantly decreased compared with post-operative BCVA (P=0.014).

The correlation between HMMH stage and pre-operative VA, post-operative BCVA, and post-operative final VA was tested using Spearman's rho test, showing statistic significance between HMMH stage and pre-operative VA, post-operative BCVA, and post-operative final VA (correlation coefficient=-0.567, P=0.000; correlation coefficient=-0.505, P=0.002; and correlation coefficient=0.472, P=0.004, respectively), suggesting that HMMH patients with increasing MH stage, the VA (including pre-operative VA, post-operative BCVA, and post-operative final VA) decreased.

4.3.11 Analysis of factors influencing HMMH surgery results

4.3.11.1 Analysis of factors influencing post-operative anatomic repair in HMMH surgery

Table 12 Analysis of factors influencing the success of first IMH surgery

	Statistical method	Chi-square	P	OR
ILM peeling	Continuity corrected chi-square	1.035	0.309	
RD after initial MH-OP	Continuity corrected chi-square	0.000	1.000	
Staining	Fisher's exact test		0.150	
Agglutination	Fisher's exact test		1.000	
Cataract surgery	Fisher's exact test		1.000	
ILM rest	Fisher's exact test	7.404	0.015	
Gas tamponade at different concentrations	Logistic regression		0.942	0.000
MH stage	Logistic regression		0.970	1.025
Course of disease	Logistic regression		0.651	1.125

Pre-operative VA	Logistic regression			0.699	1.039
Optic axial length	Logistic regression			0.508	1.152
Refraction	Logistic regression			0.970	0.000
Number of intra-ocular surgeries after initial MH-OP	Logistic regression			0.045	10.312
Total number of MH-OP	Logistic regression			0.919	999.000
Total number of intra-ocular surgeries	Logistic regression			0.045	10.312

4.3.11.2 Analysis of factors influencing post-operative visual acuity recovery after HMMH surgery

Table 13-1 Analysis of factors influencing post-operative BCVA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test	6.210		0.045	
ILM rest	Fisher's exact test	6.709		0.079	
Fundus hemorrhage	Kruskal-Wallis test	1.388		0.500	
ICG staining at different concentrations	Spearman's rho			0.408	-0.240
Gas tamponade at different concentrations	Spearman's rho			0.836	0.037
MH stage	Spearman's rho			0.891	-0.024
Course of disease	Spearman's rho			0.359	-0.158
Pre-operative VA	Spearman's rho			0.995	-0.001
Optic axial length	Spearman's rho			0.126	-0.267

Refraction	Spearman's rho		0.918	-0.018
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho		0.727	-0.060
Total number of MH-OP	Spearman's rho		0.756	-0.054
Total number of intra-ocular surgeries	Spearman's rho		0.727	-0.060
Cataract degree (final follow-up)	Spearman's rho		0.270	-0.189
Centrocecal scotoma	Spearman's rho		0.363	-0.204
Amsler grid	Spearman's rho		0.241	-0.255
ILM peeling	Wil. Sig. rank test*	-1.165	0.244	
Staining	Wil. Sig. rank test	-0.983	0.326	
ICG staining	Wil. Sig. rank test	0.000	1.000	
Agglutination	Wil. Sig. rank test	-1.446	0.148	
Cataract surgery	Wil. Sig. rank test	-0.311	0.756	
Pigment epithelial atrophy	Wil. Sig. rank test	0.631	0.528	
Pigmentation	Wil. Sig. rank test	-0.768	0.442	
Optic disc paleness	Wil. Sig. rank test	-0.036	0.971	

*Wilcoxon signed rank test

Table 13-2 Analysis of factors influencing post-operative BCVA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test	8.309		0.016	
ILM rest	Fisher's exact test	13.452		0.001	

Fundus hemorrhage	Kruskal-Wallis test	1.135		0.567	
ICG staining at different concentrations	Spearman's rho			0.408	-0.240
Gas tamponade at different concentrations	Spearman's rho			0.645	0.082
MH stage	Spearman's rho			0.853	0.032
Course of disease	Spearman's rho			0.511	-0.113
Pre-operative VA	Spearman's rho			0.570	-0.098
Optic axial length	Spearman's rho			0.810	-0.043
Refraction	Spearman's rho			0.812	0.041
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho			0.634	0.082
Total number of MH-OP	Spearman's rho			0.043	-0.339
Total number of intra-ocular surgeries	Spearman's rho			0.634	0.082
Cataract degree (final follow-up)	Spearman's rho			0.392	-0.147
Centrocecal scotoma	Spearman's rho			0.363	-0.204
Amsler grid	Spearman's rho			0.241	-0.255
ILM peeling	Wil. Sig. rank test*		-1.937	0.053	
Staining	Wil. Sig. rank test		-1.610	0.107	
ICG staining	Wil. Sig. rank test		0.000	1.000	
Agglutination	Wil. Sig. rank test		-0.850	0.395	
Cataract surgery	Wil. Sig. rank test		-1.236	0.216	
Pigment epithelial atrophy	Wil. Sig. rank test		1.545	0.122	
Pigmentation	Wil. Sig. rank test		-1.416	0.157	

Optic disc paleness	Wil. Sig. rank test	0.527	0.598	

*Wilcoxon signed rank test

Table 13-3 Analysis of factors influencing post-operative final visual acuity impairment in comparison with BCVA

	Statistical method	Chi-square	P	OR
ILM peeling	Pearson chi-square	0.08	0.777	
Staining	Pearson chi-square	0.031	0.861	
Agglutination	Pearson chi-square	2.372	0.123	
Pigment epithelial atrophy	Pearson chi-square	0.565	0.452	
Pigmentation	Pearson chi-square	0.888	0.346	
Cataract surgery	Continuity corrected chi-square	2.164	0.141	
ICG staining	Fisher's exact test		1.000	
RD after first MH-OP	Fisher's exact test		0.343	
ILM rest	Fisher's exact test	2.858	0.256	
Optic disc paleness	Fisher's exact test		0.157	
Fundus hemorrhage	Fisher's exact test	1.204	0.786	
ICG staining at different concentrations	Logistic regression		0.341	0.760
Gas tamponade at different concentrations	Logistic regression		0.828	1.141
MH stage	Logistic regression		0.889	0.932
Course of disease	Logistic regression		0.915	1.022
Pre-operative VA	Logistic regression		0.808	1.018
Optic axial length	Logistic regression		0.815	0.963

Refraction	Logistic regression	0.586	0.525
Number of intra-ocular surgeries after initial MH-OP	Logistic regression	0.702	0.858
Total number of MH-OP	Logistic regression	0.624	1.630
Total number of intra-ocular surgery	Logistic regression	0.702	0.858
Cataract degree (final follow-up)	Logistic regression	0.550	2.400
Centrocecal scotoma	Logistic regression	0.080	0.356
Amsler grid	Logistic regression	0.029	0.265

4.4 TMH group

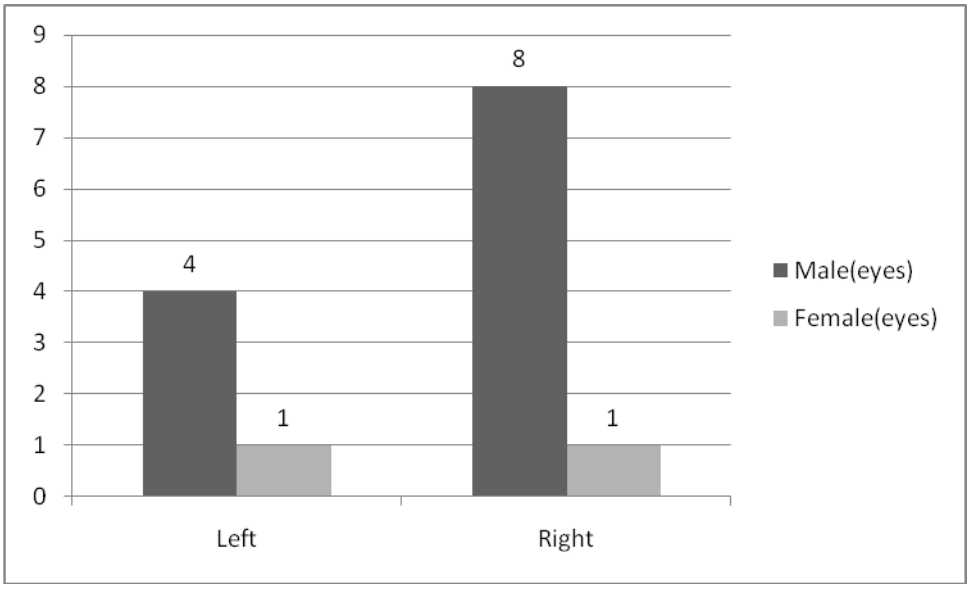
4.4.1 General clinical data of TMH

Fourteen eyes of 14 patients were included. Among the 14 patients, 12 were males (85.7%) and 2 were females (14.3%), with an average age of 35.0±21.94years (range, 35.0~71.0 years) and a mean follow-up of 48.29±46.42 months (range, 4~163months). Of the 14 patients, only 1female (7.1%) had bilateral lesions; she underwent unilateral surgery in our hospital. Among the patients who had unilateral lesions, 12 were males (85.7%) and 1 was a female (7.1%).

The incidence of unilateral or bilateral lesions had no gender differences, as confirmed by Pearson's chi-square test (P = 0.143 >0.05; [Fisher's exact test]). The age of unilateral MH patients was 32.46±20.59 years (range, 8.0~71.0 years). The patients with bilateral lesions underwent initial MH surgery as part of our research at an average age of 68.0 years. An independent samples t-test with Levene's test for equality of variances for the comparison of the age difference between male and female patients showed that two subsets of patients were derived from the population of the same age (F=0.025, P = 0.887 >0.05).The incidence of TMH among males and females showed no significant age difference (t=-1.125, P=0.283 >0.05). The binomial

non-parametric test (Npar test) showed that the incidence of TMH in patients with single or bilateral lesions was significantly higher in males than females (P = 0.013 <0.05); however, the incidence of right or left MH showed no gender difference, as confirmed by Fisher's exact test (P = 1.000 >0.05; Fig. 21).

Fig. 21 Incidence of TMH



4.4.2 Stadium of TMH

Table 14 Stadium in every TMH operation

Stadium	1st MH OP	2nd MH OP
I		
II		
III	6	1
IV	8	3
Total	14	4

Binary logistic regression showed that the initial MH stadium had no significant connection with the initial result of the surgery (P = 0.9337 >0.05).

4.4.3 Course of TMH

Table 15-1 Course of TMH

Course	Frequency	Percentage
2 (<1month)	7	50.0
3 (1～3months)	3	21.4
5 (6～12months)	1	7.15
6 (12～36months)	2	14.3
7 (unknown)	1	7.15
Total	14	100

Table 15-2 Relationship between initial success rate and TMH course

Case	Course of TMH					Total	Logistic regression
	2	3	5	6	7		
Succeed	5	0	1	2	1	9	
Fail	2	3	0	0	0	5	P=0.2667
Total	7	3	1	2	1	14	

Binary logistic regression showed that the history of TMH was not significantly associated with the success rate of MH surgery (P = 0.2667 [>0.05]).

4.4.4 Success rate of TMH surgery

After initial surgery, the success rate was 64.3% (9 eyes), with 1 eye requiring no further surgery; however, 4 eyes underwent a second surgery, all of which achieved anatomic closure of MHs. The MHs were closed in 13 (92.9%) eyes after $\geq$ 1 operations，while 1 (7.1%) eye remained open.

4.4.5 Refraction and optic axial length of the operated eyes in TMH

group

The average optic axial length of the patients in this group was 23.36±1.04mm, (range, 22.18~25.31mm).

Refraction	Frequency	Percentage	Cumulative frequency	Cumulative percentage
3 = 0~-3.0 Sphere	4	28.6	4	28.6
4 = Normal	7	50.0	11	78.6
5 = 0~+3.0 Sphere	3	21.4	264	100.0

4.4.6 Relationship between cataract and TMH surgeries

	Case	Percentage
No cataract surgery	7	50.0%
With 1st MH-OP	1	7.15%
Before 2nd MH-OP	5	35.7%
With 2nd MH-OP	1	7.15%
Total	14	100%

4.4.7 Surgical details of TMH-OP

	1st OP (case/percent)	**2nd OP** (case/percent)
ILM peeling		
None	3/14(21.4%)	1/4(25.0%)
ILM peeling	11/14(78.6%)	3/4(75.0%)
Dye		
None	8/14(57.1%)	0
ICG, normal concentration	2/14(14.3%)	1/4(25.0%)
ICG, dilute 1: 3	4/14(28.6%)	3/4(75.0%)
Agglutination		

None	1/14(7.1%)	0
Autologous thrombocytes	13/14(92.9%)	4/4(100.0%)
Intravitreal tamponade		
30% SF6	5/14(35.7%)	1/4(25.0%)
25% SF6	8/14(57.1%)	3/4(75.0%)
Silicone oil	1/14(7.1%)	0
Endocryoretinopexy		
Peripheral retinal hole	3/14(21.4%)	0
Exocryoretinopexy	6/14(42.9%)	0
Retinectomy	1/14(7.1%)	0
Encircling	1/14(7.1%)	0
Perfluorodecalin	1/14(7.1%)	0

The MH was closed in 9 eyes after the first operation and the MH was closed in 3 eyes not undergoing ILM peeling. Among the failed 5 eyes, 3 had ILM rest and underwent ILM peeling with the assistance of ICG staining in the second operation and the MH was closed; the other 2 eyes underwent whole ILM peeling, but 1 eye had PVR and MH relapsed and was then closed in the second operation, the other one MH was not closed and the reasons remain unclear, within the observation period, the second operation was not performed.

4.4.8 Complications of TMH surgery (intra- and post-operative)

	1st OP	**2nd OP**
	(case/percent)	(case/percent)
Iatrogenic retinal hole (peripheral)	2/14(14.3%)	0
Lens touch during operation		
Mild, no need to handle	1/14(7.1%)	0
Cataract	7/14(50.0%)	2/4(50.0%)

ILM rest after peeling	3/14(21.4%)	0
ILM remain (without peeling)	3/14(21.4%)	0
Retinal hemorrhage	0	1/4(25.0%)
Vitreous hemorrhage, post-operatively	1/14 (7.1%)	1/4(25.0%)
Ocular hypertension		
None	1/14(7.1%)	0
<30mmHg	5/14(35.7%)	1/4(25.0%)
>30mmHg	8/14(57.1%)	3/4(75.0%)
RD	2/14(14.3%)	0
Peripheral retinal hole		
New hole	1/14 (7.1%)	0
PVR	3/14(21.4%)	0
Macular ERM	3/14(21.4%)	0

4.4.9 History of other surgeries in the eyes of TMH

Nine eyes (64.3%) underwent only MH-OP, while the remaining eyes had other intra-ocular surgery or surgeries in addition to MH-OP. Three eyes (21.4%) had 1, 1 eye (14.3%) had 2, and 1eye (7.1%) had 5 intra-ocular surgeries. Other intra-ocular surgeries were all performed after the initial MH-OP within the observation period.

Table 16 After first TMH-OP

Diagnosis	Eyes undergo surgery after 1st TMH-OP				
	1st	2nd	3rd	4th	5th
Cataract	2	1			
RRD	1				
Retinal re-detachment	1	1	1	1	1
Aphakia	1				
Total	5	2	1	1	1

4.4.10 Visual outcomes of TMH surgery

Distance vision

	Pre-operative	Best VA post-operatively	Final VA
<0.1	2 (14.3%)	2 (14.3%)	5 (35.7%)
0.1~0.4	12 (85.7%)	8 (57.1%)	6 (42.9%)
≥0.4	0	4 (28.6%)	3 (21.4%)

Distance visual outcomes

	BCVA pre-operatively	Final VA pre-operatively	Final VA-BCVA
Improved	10 (71.4%)	7 (50.0%)	----
Stable	0	0	8 (57.1%)
Worse	4 (28.6%)	7 (50.0%)	6 (42.9%)
*P*value	0.066	0.671	0.014
t	2.006	-0.434	-2.826

(Post-operative BCVA, final VA, and pre-operative VA showed no significant differences, and the final VA was decreased compared with the BCVA)

Post-operatively, 10 (71.4%) and 7 (50.0%) eyes had improved distance vision on one visit and the final visit, respectively**.** Visual acuity ≥0.4 was achieved in 4(28.6%) and 3 (21.4%) eyes on one and the final post-operative visit, respectively, while 5 (35.7%) eyes had a VA < 0.1. Post-operative final VA improved in 7 (50.0%) eyes and was worse in 7 (50.0%) eyes. Post-operative BCVA and the final VA were not significantly better than the pre-operative (P=0.066 and P=0.671, respectively) values; however, compared with BCVA, 6 eyes had worse VA on the final visit and the final VA was significantly decreased compared with BCVA (P=0.014). The correlation between IMH stage and pre-operative VA, post-operative BCVA, and post-operative final VA was tested using Spearman's rho test; there was no statistically significant difference between HMMH stage and the pre-operative VA, post-operative BCVA, and post-operative final VA (P=0.133，P=0.493，and P=0.855, respectively).

4.4.11 Analysis of factors influencing TMH surgery results

4.4.11.1 Analysis of factors influencing post-operative anatomic repair in TMH surgery

Table 17 Analysis of factors influencing the success of first TMH-OP

	Statistical method	Chi-square	P	OR
Staining	Pearson chi-square	0.782	0.376	
Cataract surgery	Pearson chi-square	0.311	0.577	
ILM peeling	Fisher's exact test		0.258	
Agglutination	Fisher's exact test		1.000	
RD after initial MH-OP	Fisher's exact test		0.505	
ILM rest	Fisher's exact test	6.169	0.055	
ICG staining at different concentrations	Logistic regression		0.547	0.760
Gas tamponade at different concentrations	Logistic regression		0.295	0.250
MH stage	Logistic regression		0.934	0.000
Course of disease	Logistic regression		0.267	0.617
Pre-operative VA	Logistic regression		0.093	1.792
Optic axial length	Logistic regression		0.234	2.766
Refraction	Logistic regression		0.298	2.466
Number of intra-ocular surgeries after initial MH-OP	Logistic regression		0.361	0.385
Total number of MH-OP	Logistic regression		0.952	999.000
Total number of intra-ocular surgeries	Logistic regression		0.361	0.385

Table 17-2 Analysis of factors influencing final closure in TMH

	Statistical method	Chi-square	P	OR
ILM peeling	Fisher's exact test		1.000	
Staining	Fisher's exact test		0.455	
Tamponade gas/silicone oil	Fisher's exact test		1.000	
Agglutination	Fisher's exact test		1.000	
Cataract surgery	Fisher's exact test		1.000	
RD after initial MH-OP	Fisher's exact test		1.000	
ILM rest	Fisher's exact test	1.232	1.000	
Gas tamponade at different concentrations	Logistic regression		0.948	999.000
MH stage	Logistic regression		0.956	999.000
Course of disease	Logistic regression		0.834	1.149
Pre-operative VA	Logistic regression		0.608	0.813
Optic axial length	Logistic regression		0.240	0.146
Refraction	Logistic regression		0.916	0.856
Number of intra-ocular surgeries after initial MH-OP	Logistic regression		0.826	0.866
Total number of MH-OP	Logistic regression		0.956	999.000
Total number of intra-ocular surgeries	Logistic regression		0.826	0.866

4.4.11.2 Analysis of factors influencing post-operative visual acuity recovery after TMH surgery

Table 18-1 Analysis of factors influencing post-operative BCVA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test			0.505	
ILM rest	Fisher's exact test	3.129		0.245	
ICG staining at different concentrations	Spearman's rho			0.633	0.250
Gas tamponade at different concentrations	Spearman's rho			0.064	0.527
MH stage	Spearman's rho			0.145	0.411
Course of disease	Spearman's rho			0.886	-0.042
Pre-operative VA	Spearman's rho			0.2075	-0.359
Optic axial length	Spearman's rho			0.599	0.190
Refraction	Spearman's rho			0.828	-0.064
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho			0.876	0.046
Total number of MH-OP	Spearman's rho			0.012	-0.650
Total number of intra-ocular surgeries	Spearman's rho			0.876	0.046
Cataract degree (final follow-up)	Spearman's rho			0.297	-0.300
Centrocecal scotoma	Spearman's rho			0.013	-0.817
Amsler grid	Spearman's rho			0.133	-0.459

ILM peeling	Wil. Sig. rank test*	-0.099	0.921
Staining	Wil. Sig. rank test	0.354	0.724
Tamponade silicon oil/gas	Wil. Sig. rank test	0.474	0.635
Agglutination	Wil. Sig. rank test	0.474	0.635
Cataract surgery	Wil. Sig. rank test	0.000	1.000
Pigment epithelial atrophy	Wil. Sig. rank test	-0.247	0.805
Pigmentation	Wil. Sig. rank test	-0.247	0.805
Fundus hemorrhage	Wil. Sig. rank test	-1.423	0.155
Optic disc paleness	Wil. Sig. rank test	0.090	0.928

*Wilcoxon signed rank test

Table 18-2 Analysis of factors influencing post-operative final VA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
ILM rest	Fisher's exact test	4.879		0.143	
RD after initial MH-OP	Fisher's exact test			1.000	
Optic axial length	Spearman's rho			0.774	-0.104
Preoperative VA	Spearman's rho			0.258	-0.324
Refraction	Spearman's rho			0.316	-0.289
Total number of intra-ocular surgeries	Spearman's rho			0.724	0.104
Gas tamponade at different concentrations	Spearman's rho			0.471	0.220
ICG staining at different concentrations	Spearman's rho			1.000	0.000
Course of disease	Spearman's rho			0.603	-0.152
Cataract degree (final	Spearman's rho			0.271	-0.316

follow-up)				
Total number of MH-OP	Spearman's rho		0.015	-0.632
MH stage	Spearman's rho		0.317	0.289
Amsler grid	Spearman's rho		1.000	0.000
Centrocecal scotoma	Spearman's rho		0.390	-0.354
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho		0.724	0.104
Agglutination	Wil. Sig. rank test*	0.857	0.391	
Staining	Wil. Sig. rank test	0.211	0.833	
Tamponade silicon oil/gas	Wil. Sig. rank test	0.857	0.391	
Cataract surgery	Wil. Sig. rank test	0.441	0.659	
Optic disc paleness	Wil. Sig. rank test	0.000	1.000	
Pigment epithelial atrophy	Wil. Sig. rank test	0.000	1.000	
Pigmentation	Wil. Sig. rank test	0.000	1.000	
Fundus hemorrhage	Wil. Sig. rank test	-0.857	0.391	
ILM peeling	Wil. Sig. rank test	-0.538	0.591	

*Wilcoxon signed rank test

Table 18-3 Analysis of factors influencing post-operative final VA impairment in comparison with BCVA

	Statistical method	Chi-square	P	OR
Staining	Pearson chi-square	0.244	0.621	
Cataract surgery	Pearson chi-square	1.167	0.280	
Pigment epithelial atrophy	Pearson chi-square	0.389	0.533	
Pigmentation	Pearson chi-square	2.431	0.119	
Optic disc paleness	Pearson chi-square	2.363	0.124	

ILM peeling	Fisher's exact test		0.055	
Tamponade silicon oil/gas	Fisher's exact test		0.429	
Agglutination	Fisher's exact test		0.429	
RD after initial MH-OP	Fisher's exact test		0.165	
ILM rest	Fisher's exact test	4.654	0.119	
Fundus hemorrhage	Fisher's exact test		0.429	
ICG staining at different concentrations	Logistic regression		0.547	0.760
Gas tamponade at different concentrations	Logistic regression		0.928	1.111
MH stage	Logistic regression		0.535	2.000
Course of disease	Logistic regression		0.074	2.241
Pre-operative VA	Logistic regression		0.287	0.836
Optic axial length	Logistic regression		0.571	0.637
Refraction	Logistic regression		0.743	1.289
Number of intra-ocular surgery after initial MH-OP	Logistic regression		0.246	2.656
Total number of MH-OP	Logistic regression		0.733	1.500
Total number of intra-ocular surgeries	Logistic regression		0.246	2.656
Cataract degree (final follow-up)	Logistic regression		0.733	1.500
Centrocecal scotoma	Logistic regression		0.328	0.305
Amsler grid	Logistic regression		0.346	0.723

4.5 SMH group

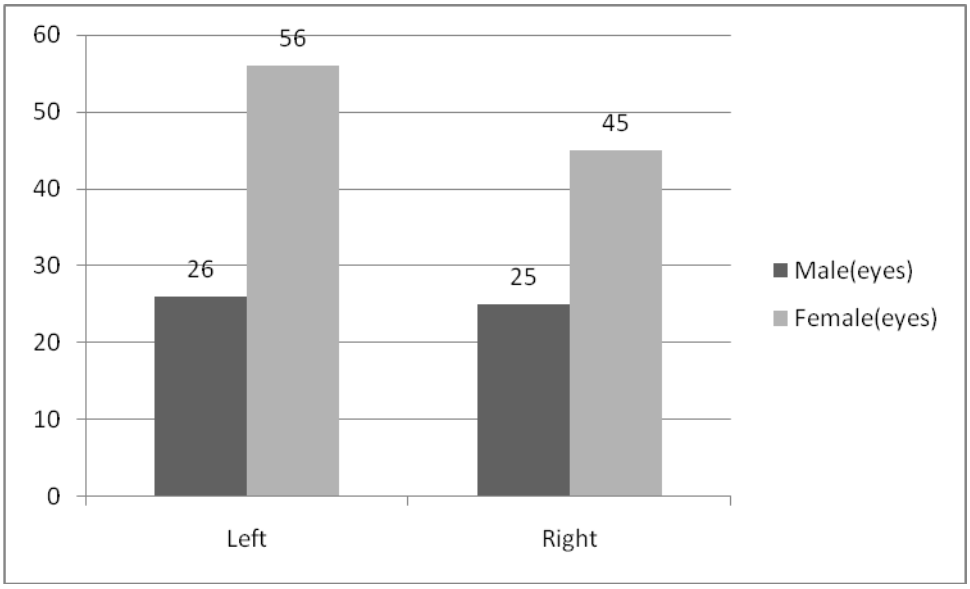
4.5.1 General clinical data of SMH

One hundred fifty-two eyes of 147 patients were included. Among the 152 patients,

48 were males (32.7%) and 99 were females (67.3%), with an average age of 65.73±6.85 years (range, 29.0~78 years) and a mean follow-up of 40.03±33.75 months (range, 3~156 months). Of 147 patients, 35 (23.8%) had bilateral lesions, including 13 (8.8%) males and 22 (15.0%) females. Among the 35 patients, 5 underwent bilateral MH surgery in our hospital, including 3 males and 2 females; 30 patients underwent unilateral surgery in our hospital, including 10 males and 20 females. Among the patients who had unilateral lesions, 35 were males (23.8%) and 77 were females (52.4%).

The incidence of unilateral or bilateral lesions showed no gender differences, as confirmed by Pearson's chi-square test (Pearson's χ^2 = 0.421, *P* = 0.516 >0.05).The age of unilateral MH patients was 65.02±7.51 years (range, 29.0-78.0 years). The patients with bilateral lesions who underwent initial MH surgery as part of our research had an average age of 67.72±3.99 years (range, 58.0-74.0 years). An independent samples t-test with Levene's test for equality of variances for the comparison of the age difference between patients with unilateral and bilateral lesions showed that two subsets of patients were derived from the population of different ages (F=4.837, *P* = 0.029 <0.05), thus patients with bilateral SMH were older than patients with unilateral SMH (t=-2.841, P=0.005 <0.05). The binomial non-parametric test (Npar test) showed that the incidence of SMH in patients with single or bilateral lesions was also significantly higher in females than males (*P* = 0.000 [<0.05]); however, the incidence of right or left MH had no gender differences, as confirmed by Pearson's chi-square test (χ^2 =0.272, *P* = 0.602 >0.05; Fig.22).

Fig.22. Incidence of SMH



4.5.2 Stadium of SMH

Table 19 Stadium in every SMH operation

Stadium	1st MH OP	2nd MH OP	3rd MH OP
I	3		
II	31		
III	77	2	
IV	41	2	1
Total	152	4	1

Binary logistic regression showed that the initial MH stadium had no significant connection with the initial result of surgery (P = 0.6376 >0.05).

4.5.3 Course of SMH

Table 20-1 Course of SMH

Course	Frequency			Percentage
	Unilateral	Bilateral	Total	
1 (<1week)	8	4	12	7.9
2 (<1month)	20	7	27	17.8
3 (1～3months)	31	8	39	25.7
4 (3～6months)	10	8	18	11.8
5 (6～12months)	18	9	27	17.8
6 (12～36months)	25	4	29	19.1
Total	112	40	152	100

Table 20-2 Relationship between initial success rate and SMH course

Case	Course of SMH						Total	Logistic regression
	1	2	3	4	5	6		
Succeed	11	25	38	17	27	28	146	
Fail	1	2	1	1	0	1	6	P=0.2748
Total	12	27	39	18	27	29	152	

Binary logistic regression showed that the history of SMH was not significantly associated with the success rate of MH surgery (P = 0.2748 >0.05).

4.5.4 Success rate of SMH surgery

After initial surgery, the success rate was 96.1% (146 eyes), with 2 eyes requiring no further surgery; however, 4 eyes underwent a second surgery, with a success rate of 75.0% (3 eyes). One eye had a third surgery and achieved anatomic closure of the MH. The MH was closed in 150 (98.7%) eyes after $\geq$ 1 operation，while 2 (1.3%) eyes re-opened after a period of time post-operatively.

4.5.5 Refraction and optic axial length of operated eyes in the SMH group

The average optic axial length of the patients in this group was 23.25±1.12 mm, (range, 20.89~27.10 mm).

Refraction	Frequency	Percent	Cumulative frequency	Cumulative percentage
1 = <-6.0 Sphere	5	3.3	5	3.3
2 = -3.0~-6.0 Sphere	10	6.6	15	9.9
3 = 0~-3.0 Sphere	33	21.7	48	31.6
4 = Normal	14	9.2	62	40.8
5 = 0~+3.0 Sphere	74	48.7	136	89.5
6 = >+3.0 Sphere	15	9.9	151	99.3
7 = Unclear	1	0.7	152	100.0

4.5.6 Relationship between cataract and SMH surgeries

	Case	Percent
No cataract surgery	23	15.1%
With 1st MH-OP	39	25.7%
Before 2nd MH-OP	86	56.6%
With 2nd MH-OP	2	1.3%
Before 3rd MH-OP	2	1.3%
Total	152	100%

4.5.7 Surgical details of SMH-OP

	1st OP	**2nd OP**	**3rd OP**
	(case/percent)	(case/percent)	(case/percent)
ILM peeling			
None	12/152(7.9%)	1/4(25.0%)	0
ILM peeling	140/152(92.1%)	3/4(75.0%)	1/1(100.0%)
Dye			
None	57/152(37.5%)	2/4(50.0%)	0
ICG, normal concentration	37/152(24.3%)	1/4(25.0%)	0
ICG, dilute 1:2	1/152(0.7%)	0	0
ICG, dilute 1:3	57/152(37.5%)	0	1/1(100.0%)
TA	0	1/4(25.0%)	0
Agglutination			
None	11/152(7.2%)	1/4(25.0%)	0
Autologous thrombocytes	137/152(90.1%)	3/4(75.0%)	1/1(100%)
Autologous whole blood	4/152(2.6%)	0	0
Intravitreal tamponade			
None	0	0	0
40%SF6	3/152(2.0%)	0	0
35% SF6	1/152(0.7%)	0	0
30% SF6	41/152(27.0%)	1/4(25.0%)	1/1(100.0%)
25% SF6	104/152(68.4%)	2/4(50.0%)	0
20%SF6	3/152(2.0%)	1/4(25.0%)	0
Endocryoretinopexy	14/152(9.2%)	0	0
Exocryoretinopexy	53/152(34.9%)	1/4(25.0%)	0
Endolaser-photocoagulation	3/152(2.0%)	0	0
Perfluorodecalin	2/152(1.3%)	0	0

The MH was closed in 146 eyes after the first operation. Three of 6 failed eyes had

no ILM rest. Two eyes had no surgical treatment during the follow-up and the MH was closed in 1 eye in the second operation. Another 3 eyes had ILM rest. During the second operation, these eyes underwent ILM peeling with the assistance of ICG staining. One eye still had no whole ILM peeling; the MH was not closed in this eye and closed after the third operation. The other 2 eyes had whole ILM peeling after the second operation and the MH was closed.

4.5.8 Complications of SMH surgery (intra- and post-operative)

	1st OP	**2nd OP**	**3rd OP**
	(case/percent)	(case/percent)	(case/percent)
Iatrogenic retinal hole (peripheral)	3/152(2.0%)	0	0
Lens touch during operation			
Mild, no need to handle	1/152(0.7%)	0	0
Cataract	106/152(69.7%)	0	0
ILM rest after peeling	20/152(13.2%)	2/4(50.0%)	0
ILM remain (without peeling)	12/152(7.9)	1/4(25.0%)	0
Hyphema, post-operative	1/152(0.7%)	0	0
Retinal hemorrhage	6/152(3.9%)	0	0
Vitreous hemorrhage, post-operatively	3/152 (2.0%)	0	0
Ocular hypertension			
None	14/152(9.2%)	1/4(25.0%)	0
<30mmHg	43/152(28.3%)	1/4(25.0%)	1/1(100.0%)
>30mmHg	95/152(62.5%)	2/4(50.0%)	0
RD	6/152(3.9%)	0	0
Peripheral retinal hole			
New hole	5/152(3.3%)	0	0
New and old holes	1/152(0.7%)	0	0

PVR	3/152(2.0%)	0	0
Macular ERM	17/152(11.2%)	1/4(25.0%)	0
Macular pucker	2/152(1.3%)	0	0
Aftercataract	4/152(2.6%)	1/4(25.0%)	0
Fibrin exudation	3/152(2.0%)	0	0
Gas prolapse	0	1/4(25.0%)	0
Secondary glaucoma	1/152(0.7%)	0	0
Visual field defect	4/152(2.6%)	0	0
Uveitis	1/152(0.7%)	0	0
Choroidal detachment	1/152(0.7%)	0	0
Fistula of corneoscleral tunnel	1/152(0.7%)	0	0

4.5.9 History of other surgeries in eyes of SMH

Sixty-one eyes (40.1%) underwent only MH-OP, while the remaining eyes had other intra-ocular surgery or surgeries in addition to MH-OP. Seventy-six eyes had 1(50.0%), 10 eyes had 2(6.6%), and 5 eyes had 3(3.3%) intra-ocular surgeries.

Table 21-1 After first SMH-OP

Diagnosis	Eyes undergoing surgery after 1st MH-OP		
	1st	2nd	3rd
Cataract	79	3	
RRD	3		
RD	1	1	
Rhegmatogenous retinal re-detachment	1		
Silicon oil removal			1
Aftercataract	1	11	1

IOL dislocation			1
Aphakia	1		
Endophthalmitis		1	
Peripheral retinal hole		1	
Cystoid macular edema	1		
Total	90	17	3

Table 21-2 After 2nd SMH-OP

Diagnosis	Eyes undergoing surgery after 2nd MH-OP		
	1st	2nd	3rd
Cataract	2		
Total	2	0	0

4.5.10 Visual outcomes of SMH surgery

Distance vision

	Pre-operative	Best VA post-operatively	Final VA
<0.1	17 (11.2%)	3 (2.0%)	6 (3.9%)
0.1~0.4	94 (61.8%)	52 (34.2%)	49 (32.2%)
≥0.4	41 (27.0%)	97 (63.8%)	97 (63.8%)

Distance visual outcome

	BCVA pre-operatively	Final VA pre-operatively	Final VA-BCVA
Improved	121 (79.6%)	107 (70.4%)	----
Stable	15 (9.9%)	17 (11.2%)	103 (67.8%)
Worse	16 (10.5%)	28 (18.4%)	49 (32.2%)
P Value	0.000	0.000	0.000
t	12.718	8.499	-5.984

Post-operatively, 121 (79.6%) and 107 (70.4%) eyes had improved distance vision on 1 visit and the final visit, respectively**.** Visual acuity ≥ 0.4 was achieved in 97 (63.8%) eyes on one and the final post-operative visit, respectively, while 6 (3.9%) eyes had VA < 0.1. Post-operative final VA improved in 107 (70.4%) eyes remained stable in 17 (11.2%) and worse in 28 (18.4%) eyes. Post-operative BCVA and final VA were significantly better than the pre-operative (P=0.000) values; however, compared with BCVA, 49 (32.2%) eyes had worse VA on the final visit; the final VA significantly decreased compared with post-operative BCVA (P=0.000).

The correlation between the SMH stage and pre-operative VA, post-operative BCVA, and post-operative final VA was tested using Spearman's rho test, showing statistical significance between the SMH stage and the pre-operative VA, post-operative BCVA, and post-operative final VA (P=0.000, P=0.017, and P=0.021, respectively). The correlation coefficients were -0.479, -0.193, and -0.188, respectively.

4.5.11 Analysis of factors influencing SMH surgery results

4.5.11.1 Analysis of factors influencing post-operative anatomic repair in SMH surgery

Table 22-1 Analysis of factors influencing the success of first SMH-OP

	Statistical method	Chi-square	P	OR
ILM peeling	Fisher's exact test		1.000	
Staining	Fisher's exact test		0.013	
Agglutination	Fisher's exact test		0.368	
Different agglutinations	Fisher's exact test		1.000	
Cataract surgery	Fisher's exact test		0.592	
RD after initial MH-OP	Fisher's exact test		1.000	
ILM rest	Fisher's exact test	11.230	0.004	
ICG staining at different	Logistic regression		0.948	14.251

concentrations				
Gas tamponade at different concentrations	Logistic regression		0.531	0.592
MH stage	Logistic regression		0.638	1.315
Course of disease	Logistic regression		0.275	0.736
Pre-operative VA	Logistic regression		0.539	0.933
Optic axial length	Logistic regression		0.367	0.667
Refraction	Logistic regression		0.271	1.565
Number of intra-ocular surgeries after initial MH-OP	Logistic regression		0.195	0.353
Total number of MH-OP	Logistic regression		0.999	999.000
Total number of intra-ocular surgeries	Logistic regression		0.814	0.868

Table 22-2 Analysis of factors influencing final closure in SMH

	Statistical method	Chi-square	P	OR
ILM peeling	Fisher's exact test		1.000	
Staining	Fisher's exact test		0.102	
ICG at different concentrations	Fisher's exact test	3.375	1.000	
Agglutination	Fisher's exact test		1.000	
Different agglutinations	Fisher's exact test		1.000	
Cataract surgery	Fisher's exact test		1.000	
RD after initial MH-OP	Fisher's exact test		1.000	
ILM rest	Fisher's exact test	0.809	1.000	
Gas tamponade at different concentrations	Logistic regression		0.687	0.689

MH stage	Logistic regression	0.960	1.049
Course of disease	Logistic regression	0.851	1.088
Pre-operative VA	Logistic regression	0.829	1.043
Optic axial length	Logistic regression	0.250	2.764
Refraction	Logistic regression	0.156	0.252
Number of intra-ocular surgeries after initial MH-OP	Logistic regression	0.583	0.633
Total number of MH-OP	Logistic regression	0.986	999.000
Total number of intra-ocular surgeries	Logistic regression	0.605	0.645

4.5.11.2 Analysis of factors influencing post-operative VA recovery after SMH surgery

Table 23-1 Analysis of factors influencing post-operative BCVA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test	11.751		0.003	
ILM rest	Fisher's exact test	2.166		0.696	
Fundus hemorrhage	Kruskal-Wallis test	0.792		0.673	
ICG staining at different concentrations	Spearman's rho			0.048	0.204
Gas tamponade at different concentrations	Spearman's rho			0.855	0.015
MH stage	Spearman's rho			0.113	0.129
Course of disease	Spearman's rho			0.911	0.009

Pre-operative VA	Spearman's rho		0.033	-0.173
Optic axial length	Spearman's rho		0.589	0.045
Refraction	Spearman's rho		0.590	-0.044
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho		0.003	0.236
Total number of MH-OP	Spearman's rho		0.311	0.083
Total number of intra-ocular surgeries	Spearman's rho		0.002	0.254
Cataract degree (final follow-up)	Spearman's rho		0.113	-0.129
Centrocecal scotoma	Spearman's rho		0.185	-0.125
Amsler grid	Spearman's rho		0.004	-0.262
ILM peeling	Wil. Sig. rank test*	1.804	0.071	
Staining	Wil.Sig. rank test	0.092	0.926	
Agglutination	Wil. Sig. rank test	-0.648	0.517	
Different agglutinations	Wil. Sig. rank test	-0.125	0.901	
Cataract surgery	Wil. Sig. rank test	-1.438	0.150	
Pigment epithelial atrophy	Wil. Sig. rank test	-1.742	0.082	
Pigmentation	Wil. Sig. rank test	-1.480	0.139	
Optic disc paleness	Wil. Sig. rank test	-0.049	0.961	
Secondary glaucoma	Wil. Sig. rank test	0.487	0.627	
Visual field defect	Wil. Sig. rank test	-1.712	0.087	

*Wilcoxon signed rank test

Table 23-2 Analysis of factors influencing post-operative final VA improvement in comparison with pre-operative VA

	Statistical method	Chi-square	Z	P	Correlation coefficients
RD after initial MH-OP	Fisher's exact test	6.843		0.024	
ILM rest	Fisher's exact test	1.435		0.863	
Fundus hemorrhage	Kruskal-Wallis test	1.637		0.441	
ICG staining at different concentrations	Spearman's rho			0.170	0.142
Gas tamponade at different concentrations	Spearman's rho			0.437	0.063
MH stage	Spearman's rho			0.158	0.115
Course of disease	Spearman's rho			0.362	0.074
Pre-operative VA	Spearman's rho			0.035	-0.171
Optic axial length	Spearman's rho			0.422	0.067
Refraction	Spearman's rho			0.243	-0.095
Number of intra-ocular surgeries after initial MH-OP	Spearman's rho			0.266	0.091
Total number of MH-OP	Spearman's rho			0.931	0.007
Total number of intra-ocular surgeries	Spearman's rho			0.174	0.111
Cataract degree (final follow-up)	Spearman's rho			0.253	-0.093
Centrocecal scotoma	Spearman's rho			0.331	-0.092
Amsler grid	Spearman's rho			0.000	-0.352

ILM peeling	Wil. Sig. rank test*	1.048	0.295
Staining	Wil. Sig. rank test	-0.209	0.835
Agglutination	Wil. Sig. rank test	-0.399	0.690
Different agglutinations	Wil. Sig. rank test	0.374	0.709
Cataract surgery	Wil. Sig. rank test	-0.977	0.328
Pigment epithelial atrophy	Wil. Sig. rank test	-1.509	0.131
Pigmentation	Wil. Sig. rank test	-1.399	0.162
Optic disc paleness	Wil. Sig. rank test	-0.662	0.508
Secondary glaucoma	Wil. Sig. rank test	-1.747	0.081
Visual field defect	Wil. Sig. rank test	-2.016	0.044

*Wilcoxon signed rank test

Table 23-3 Analysis of factors influencing post-operative final VA impairment in comparison with BCVA

	Statistical method	Chi-square	P	OR
Staining	Pearson chi-square	3.585	0.058	
Cataract surgery	Pearson chi-square	3.015	0.082	
ILM rest	Pearson chi-square	1.26	0.543	
Pigment epithelial atrophy	Pearson chi-square	3.363	0.067	
ILM peeling	Continuity corrected chi-square	0.165	0.684	
Agglutination	Continuity corrected chi-square	0.001	0.975	
Pigmentation	Continuity corrected chi-square	0.025	0.875	
Optic disc paleness	Continuity corrected chi-square	0.862	0.353	
Visual field defect	Continuity corrected chi-square	0.052	0.819	
Different agglutinations	Fisher's exact test		1.000	
RD after initial MH-OP	Fisher's exact test		1.000	
Secondary glaucoma	Fisher's exact test		0.322	

Fundus hemorrhage	Fisher's Exact Test	2.839	0.247	
ICG staining at different concentrations	Logistic regression		0.309	0.866
Gas tamponade at different concentrations	Logistic regression		0.618	0.866
MH stage	Logistic regression		0.763	0.932
Course of disease	Logistic regression		0.434	1.089
Pre-operative VA	Logistic regression		0.494	1.035
Optic axial length	Logistic regression		0.794	0.959
Refraction	Logistic regression		0.249	0.857
Number of intra-ocular surgeries after initial MH-OP	Logistic regression		0.658	1.110
Total number of MH-OP	Logistic regression		0.624	0.618
Total number of intra-ocular surgeries	Logistic regression		0.814	1.058
Cataract degree (final follow-up)	Logistic regression		0.156	1.944
Centrocecal scotoma	Logistic regression		0.658	0.925
Amsler grid	Logistic regression		0.131	0.767

5. Discussion

5.1 Success rate of MH surgery

There was no suitable solution for MH after the first description by Knapp[1] in 1869 until Kelly and Wendel[72] introduced the use of pars plana vitrectomy to treat this disease in 1991, and the MH closure rate reached 58%. With more and more research involving the pathologic mechanism underlying MH formation and the development of surgical technique, the postoperative closure rate of MH had reached 90%.[117, 131, 201, 202] The treatment on MH reported in the literature was more limited to a single pathogenesis, such as pure IMH, TMH, and HMMH. In the current study we summarized and compared the curative effect of MHs of different pathogeneses in the clinic setting. The results indicated that the currently adopted operative method had a good curative effect on MHs of most pathogeneses. In the current study the MH was closed in 477 (97.9%) eyes after one or more operations. The final success rates of MH surgery in the IMH, HMMH, TMH, and SMH groups were 97.5%, 100%, 92.9%, and 98.7%, respectively.

5.2 Effects of surgical procedures on MHs

5.2.1Clinical efficacy of ILM peeling in the surgical treatment of MHs

According to the theory of Gass, ILM plays a crucial role in the occurrence of IMH. ILM forms the inner border of the retina and is made up of the footplates of Müller cells. Tractional force from the posterior vitreous membrane is believed to have an effect on the neurosensory retina through the ILM. Therefore, the majority of investigators advocated ILM peeling in the treatment of MH in recent years, and the related reports were persistently published. In 1997 Smiddy et al.[203] reported a 91% closure rate of MHs after using ILM peeling, and 40% of eyes had a 0.5 or better VA. Brooks and associates[117] considered that ILM peeling can significantly improve the success rate of the MH operation, improve VA, and can reduce post-operative recurrence of MH. Al-Abdulla et al.[119] considered that the group with ILM peeling has a higher primary MH

closure rate than epiretinal dissection or no dissection in eyes; however, the final VA outcomes were similar in all groups.

A recently published meta-analysis also indicated that the obtained statistical data supported ILM peeling as the treatment of choice for patients with idiopathic stage II, III, and IV full-thickness MH and other retinal diseases, including epiretinal membrane, diabetic macular edema, and retinal vein occlusion.[204] Lezzi et al.[172] reported a wide range of ILM peeling (approximately 8000 μm in diameter) to upper and lower vascular arcade, followed by 2 fluid-air exchanges, separated by 5 min, and an air-20% SF6 exchange, without FDP, which had a good curative effect on MH. Nevertheless, there are still disputes whether or not ILM peeling should be done. In fact, many investigators have doubts about this question. Despite its clear indication in MH surgery, ILM peeling is still a traumatic procedure that has acute effects on the underlying inner retinal layers.[122] Spaide[205] observed 10 eyes with MHs, 15 eyes with ERM, and 18 eyes underwent ILM peeling. The volume-rendering image of post-operative SD-OCT showed that the inner retinal surface of 13 of 18 eyes developed pitting or dimples. Combined with the B-scan image of SD-OCT, it showed focal areas of thinning of the ganglion cell layer with decreased reflectivity from the nerve fiber layer in the areas of the dimples.[205] Some researchers believe that not all patients with MHs should undergo ILM peeling. The argument is that the vitreous tangent traction force does not exist in every case based on the causes of MH. Margherio et al.[206] reported the results of the treatment for a group of patients with MHs and compared the results with and without ILM peeling. In this group of 107 patients, the overall MH closure rate was 88%. The cases without ILM peeling had a 92% closure rate, while the rate was only 82% in the cases with peeling. Terasaki et al.[207] analysed the changes of each component of the focal ERGs in eyes before and after ILM peeling during surgery for IMH, and considered that the removal of the ILM had no adverse effect on VA. The selective delay in recovery of the focal macular ERG b-wave after surgery suggests that ILM peeling might cause a disturbance and lead to an alteration of retinal physiology in the focal macular region. Some authors consider that for most acute IMH, an entirely successful separation of the posterior vitreous membrane and macular is done and ILM

peeling is not necessary. For stage 4 MHs, old MHs, surgical failures, or recurrent cases, ILM peeling is helpful for the closure and in reducing relapse. Investigators who approved of ILM peeling inspected the tissues from the ILM of MH cases and found collagen, glial cells, macrophages, RPE cells, myofibroblasts, and astrocytes on the inner and outer surfaces of the ILM. These cells might relate to the tangential traction of MHs. ILM peeling can reduce the formation of these cells. Yoon[27] reported that tissue from stage II MHs showed cellular elements enmeshed in cortical vitreous, and tissues from stage III and IV MHs had cellular proliferation on the ILM. Yoon[27]inferred that cells, including RPE and glial cells with myofibroblastic differentiation, migrate onto the inner surface of the ILM, and with the help of contraction of posterior prefoveal vitreous, form the tangential contractile forces leading to enlargement of MHs.

Olsen[153] reported a 96% MH closure rate in a group of patients with ILM peeling, but only 71% in a group of patients without ILM peeling, which contradicted the findings of Margherio.[206] Wender[208] found that simple relief of vitreomacular traction would not lead to MH closure. With a hydrodynamic model in which MH anatomy is determined by a balance between fluid flow through the hole and fluid outflow across the retinal pigment epithelium, hydrodynamics was considered more important than tangential traction in determining the morphology of stage III MHs. Thus, MH still occurs, even after vitrectomy. Indeed, ILM peeling may be an effective way to solve the problem. Oyagi[209] reported a case of full-thickness MH with a cuff in which ILM was carefully examined during vitrectomy surgery. The ILM was stained with ICG to allow the researchers to observe the ILM more clearly. Oyagi[209] found that the ILM over the foveal area was intact, and the MH formed under an intact ILM. The question is how the MH forms without simultaneously forming a hole in the ILM. This also shows that the causes of MH are complex.

In the current study the four groups with different causes underwent ILM peeling during the operation, but did not obtain a higher success rate or better post-operative VA improvement ($P > 0.05$); however, ILM rest led to fibroplasia and relapse of the MH. In the IMH group, 23 of 42 eyes not undergoing ILM peeling had a decreased VA compared with BCVA, while 72 of 243 eyes decreased (10.179 [chi-square], $P=0.001$).

Donut-shaped ILM peeling with ILM preservation within 400 μm of the foveola for stage II MH had better MH repair and vision recovery than whole ILM peeling.[121] Non-peeling of the foveolar ILM in early stage II IMH surgery prevented inner retinal damage, restored the umbo light reflex, achieved better foveolar microstructure, and led to better final VA.[121] The new inverted ILM flap technique [141] for MH was described in 2010, to which Shin et al.[143] proposed improvements in 2014. Shin et al.[143] suggested that the inverted ILM flap technique was similar to packing a MH with a folded ILM rather than covering the MH with a true flap. Thus, Shin et al.[143] did not peel the entire ILM at the periphery of the macula, and only peeled the ILM with a size equal to MH near the MH and covered the single-layered flap of the ILM on the MH. This technique is not widely used now, but the development trend of this technique has reminded us to further consider the previous operative methods.

5.2.2 Efficacy and safety of imaging dyes for ILM peeling

Peeling of the ILM is greatly facilitated by the application of various auxiliary dyes that enhance visualization. Among the most widely used dyes are ICG, TB, and TA. Since 2006,[137] BBG has been popularized due to its better staining effect, lesser toxicity than ICG[140] and better post-operative visual prognosis.[139] During the patient data collection in this study, ICG was the most widely used in ILM peeling. Currently, at least in China, ICG is still the most commonly used dye during MH surgeries. Thus, the clinical efficacy of ICG has been the most intensively studied. More and more researchers agree that visual field defects must be concerned with the use of ICG dye, but in the literature for last 20 years it is apparent that even before the application of ICG in the last century, this complication had already been reported.[210] The post-operative intra-ocular residual time of ICG can be of several months duration, so the long-term toxicity of residual ICG on macular health is of great concern. While most ophthalmologists would agree that ICG can be toxic to the RPE, there is dissension; specifically, the RPE damage observed after dye-assisted surgery could be due to mechanical injury rather than direct ICG-mediated cell damage. The ultrastructural

analysis of peeled ILM[211] showed that both the ILM and the adjacent retinal structures, and in some areas the entire foot plates of Müller cells, were visible in the sections. Indeed, the ILM cannot be removed without disrupting Müller cells and the nerve fiber layer.[212] Wolf and associates[213] studied 37 patients (37 eyes) with MHs subjected to ICG-assisted ILM peeling and suggested that ICG-assisted peeling is safe, with satisfactory functional outcomes. In addition, the unavoidable changes in RPE structure were not associated with decreased VA or visual field defects. In fact, 70% of eyes with RPE changes actually demonstrated improved function.

In contrast, a meta-analysis comparing ILM peeling with and without ICG staining during MH surgery[214] concluded that the anatomic success was similar whether or not ICG had been applied, but that application of ICG in the treatment of MHs leads to statistically worse functional outcomes and a higher number of RPE alterations. We maintain, however, that the dye facilitates shorter operative times and reduced retinal trauma can improve the success rate of MH surgery. In the current study ICG was used as the major dye, in the MH surgeries of the four groups, while BBG and TA were only used in individual surgeries. Among the surgeries of the four groups, only the group with the use of dye in the SMH group had a higher success rate than the group without the use of dye (P=0.013). The success rate of other groups showed no statistical difference with the use of dye (P>0.05). With respect to visual prognosis, the dye-assisted operated eye in the IMH group had a lower incidence of decreased VA compared with post-operative BCVA at the final follow-up than the group without the use of dye (10.129 [chi-square], P=0.001). In the IMH group, the group with the use of undiluted ICG was more likely to have decreased final VA than the group with the use of diluted ICG (P=0.0037, OR=0.717). In the SMH group, the lower the concentration of diluted ICG, the less the improvement in post-operative BCVA (Spearman’s correlation coefficient = 0.20391, P=0.0475). Although there were some doubts about the data of these two groups, we still believe that the use of ICG is useful for MH surgeries. No adverse effect of ICG on the success rate of the four groups was obtained from the statistical data. According to the prognosis of visual function, the statistical data of IMH and SMH showed a positive function. With respect to the concentration of ICG, the high

concentration of ICG in the IMH group caused an adverse effect on visual prognosis, while the SMH group had the opposite response. Can this be explained as the direct toxicity is reduced due to the barrier action of ERM after the injection of ICG into the vitreous? The undiluted or slightly diluted ICG can better assist ILM peeling due to better staining, which reduces the unnecessary operative injury and leads to better visual function recovery.

5.2.3 Adjunctive agents

In recent years biological adjuvants have been reported to increase the success rate of MH surgery. TGF-β2 has been shown to promote the synthesis of collagen in the process of wound healing and increase adhesions involving the choroid and retina.[215, 216] Autologous concentrated platelets contain abundant TGF-β2, characterized by low cost and simple extraction. It is feasible and effective to seal MHs with autologous concentrated platelets. A French study[149] showed that the use of autologous concentrated platelets was helpful for healing MHs, but insignificant for VA in comparison with controls. Paques et al.[216] initiated a multicenter, double-masked, randomized clinical trial involving 110 eyes from four university-based ophthalmology clinics regarding the efficacy and safety of autologous platelet concentrate as an adjuvant in MH surgery. Among the 110 eyes, 53 were sealed with platelets and 57 were enrolled as controls, showing that the anatomic recovery rate was significantly higher in the platelet treatment group than the control group, although recovery in VA did not differ significantly during the follow-up period. No platelet injection-associated complications occurred. Wachtlin et al.[217] reported that the injection of one-drop fresh autologous platelet concentrate ($4x10^9$ /ml) into MH after ILM peeling in 4 pediatric patients at a mean age of 13.2 years resulted the primary closure by a single intervention in all of the patients with a marked post-operative visual improvement (grade 3-7). The surgically achieved visual improvement remained stable and no vision-threatening complications occurred during a mean follow-up period of 35.2 months. Korobelnik et al.[215] defined the effective concentration of platelets as >

1,500,000/mm^3 (1.5×10^9/ml). A cadaveric pathologic examination of patients with visual improvement, but without MH treatment, showed that collagen fibers and proliferating RPE cells sealed the periphery of the MH. Such findings proved that the increase in choroid-retina adhesion of the MH margin gave rise to visual improvement. Adhesions formed a barrier to the flow of liquid below the margin of the MH, promoted the absorption of liquid, and improved VA.[218] The development of idiopathic MH was not complicated with the loss of retinal nervous tissue at the fovea.[17] Therefore, it is rational to conclude that the use of autologous platelets following vitrectomy promotes the healing of MH and improve VA.

Although our findings were not statistically significant, the use of biological adjuvants had no influence on the success rate of the first operation ($P>0.05$). According to the statistical results of our study, the IMH group showed differences between those sealed with whole blood (4 eyes) and those sealed with autologous platelets (272 eyes; $P=0.006$); however, the operated eyes sealed with whole blood were small in number, thus this result may be biased and not accurate. Alternatively, the new inverted ILM flap technique[141-143] induced glial cell proliferation, resulting in MH filling with proliferating cells that enhance closure. Can this be considered another type of biological adjuvant?

5.3 Complications

Intra- and post-operative complications of MH surgery have been reported sporadically. In our study, iatrogenic retinal hole (peripheral), iatrogenic retinal hole (during peeling), lens touch during operation, ILM rest after peeling, retinal haemorrhage, intra- and post-operative hyphema, post-operative vitreous haemorrhage, ocular hypertension, cataract, dislocation of IOL, retinal detachment, peripheral retinal hole, infection, PVR, macular gliosis, macular pucker, after cataract, fibrin exudation, silicone oil prolapse, gas prolapse, secondary glaucoma, visual field defects, uveitis, choroidal detachment, and RPE alterations were observed.

Overall, the complications of MH were similar to the complications of other vitreous surgeries. Of all the complications, the formation or aggravation of cataracts occurred

most frequently. In the IMH group, 216 of 285 eyes had cataracts after the first MH-OP, with an incidence of 76.3%, and 11 of 29 eyes had cataracts after the second MH-OP, with an incidence of 37.9%. In HMMH, 30 of 36 eyes had cataracts after the first MH-OP, with an incidence of 83.3%. In the TMH group, 7 of 14 eyes had cataracts after the first MH-OP with an incidence of 50%, and 2 of 4 eyes had cataracts after the second MH-OP, with an incidence of 50%. In the SMH group, 106 of 152 eyes had cataracts after the first MH-OP, with an incidence of 69.7%, and 2 of 4 eyes had cataracts after the second MH-OP, with an incidence of 50%. Pediatric patients were less likely to develop cataracts than adult patients,[199] whereas patients > 50 years of age were more likely to have complications involving cataracts than patients < 50 years of age.[198] As the most common complication after intra-ocular surgery, we focus on whether or not cataract surgery after the development of cataracts will lead to re-occurrence of MH. Bhatnagar et al.[187] suggested that cataract extraction after successful vitrectomy for MH, when accompanied by CME complications, might increase the risk of MH recurrence. In the current study, a four-fold increase in the risk of MH recurrence was observed in patients undergoing cataract extraction after successful vitrectomy. In the eyes remaining phakic at the last examination, a seven-fold increase in the risk of recurrence was observed. The development of clinically-apparent CME was significantly associated with a seven-fold increase in the risk of MH recurrence in patients undergoing cataract extraction after vitrectomy treatment for MH. Christmas et al.[186] reported a MH recurrence rate of 5%. In 17 recurrent MH eyes, 10 had undergone previous cataract surgery. In only one of the patients was the recurrence associated with cataract surgery. Therefore, the recurrence of MH was thought to be rarely associated with cataract surgery. Passemard et al.[223] stated that both cataract extraction and CME were not apparent risk factors for IMH recurrence. Muselier et al.[224] proposed that synchronous or asynchronous MH and cataract surgeries were safe for patients, as cataract surgery did not increase the risk for MH recurrence, whereas the combined surgery could shorten the course of visual recovery. According to the current study, no statistical data supported the re-occurrence of MH after cataract surgery. In the IMH and SMH groups,

timely and appropriate surgery might lead to better VA recovery.

A visual field defect is a more serious and frequently reported complication. Our data also showed that visual field defects are contributing factors to poor post-operative visual recovery in the IMH group, which was not significantly associated with the intra-operative use of stain and the concentration of ICG. Visual field defects have been commonly described in MH surgery, even without the use of ICG for ILM staining. The mechanisms leading to visual field defects are thought to be as follows: (1) mechanical trauma during separation of the posterior hyaloid; (2) mechanical trauma during fluid-air exchange; (3) glaucomatous changes due to elevated intra-ocular pressure; and (4) phototoxicity.[191] Some researchers have suggested that insufflation of dry air during fluid-air exchange is the cause of visual field loss after vitrectomy in the treatment of MH. It has been noted that visual field defects predominated in the inferotemporal quadrant when the infusion cannula was located in the inferotemporal quadrant. Air from an infusion cannula located in the inferotemporal quadrant flowed directly to and damaged the superonasal retina, resulting in visual field loss in the inferotemporal quadrant. Welch et al.[225] strongly supported this hypothesis by securing an infusion cannula superiorly at the 12 o'clock position in 8 eyes undergoing MH surgery, showing a visual field defect in the superior quadrant in 4 eyes. Hutton et al.[191] arrived at a similar conclusion, and hypothesized that these changes were attributable to artificial, abrupt detachment of the cortical vitreous body, perhaps in combination with the prolonged direct contact of air bubbles with the retina. The fact that the nasal retina to the optic disk became thinner than the temporal retina could be explained by a direct flow of dry air to the nasal retina. An epiretinal membrane specimen of a 43-year-old male patient who suffered from metamorphopsia and a visual defect in his right eye for a period of 2 years was examined by using a transmission electron microscope. This specimen showed adhesions between the epiretinal membrane and the axons of the nerve fiber layer in the area corresponding to the previous ILM defect.[226] The authors suggested that the adhesions between epiretinal membranes and retinal tissues in the area of the internal limiting lamina defect might damage the nerve fiber layer and result in a visual field defect after epiretinal ILM peeling. Recently,

in Paris, France, Tadayoni et al.[227] reported that the dissociated optic nerve fiber layer occurred frequently after the removal of an epiretinal membrane, suggesting that this feature was due to the extensive peeling of the ILM. In the current study, 4 patients each in the IMH and SMH groups developed visual field defects, with a lower incidence than other complications which developed during other intra-ocular surgeries. The damage caused by mechanical injury and ICG staining in the process of surgical procedure should be evaluated in detail.

5.4 Post-operative VA recovery and contributing factors

The post-operative closure of MHs may result in varying degrees of improvement of VA. Different degrees of post-operative improvement and outcome of VA have been reported by different authors. Such differences are attributed to multiple factors, such as age, gender, baseline VA, cause of MH, history of MH, stage, concomitant local retinal detachment, ocular axial length, MH basal RPE function, differences in surgical procedure, and direct procedural injuries, which were directly or indirectly associated with the post-operative recovery of VA. Informing patients of the expected VA and visual improvement before surgery is ideal, but predicting post-operative visual outcomes is difficult because a large number of factors are involved.[219] In 2003 Sasahara et al.[220] reported a case of secondary MH from laser injury. A 52-year-old man had his right eye injured by Ti:Sapphire; the VA decreased to 0.3, initially exhibiting focal macular pigment epithelial atrophy without concomitant posterior vitreous detachment. An OCT examination only identified a high-density reflection at the macular fovea, without concomitant macular contraction. After 53 days, however, the follow-up examination identified a full-thickness hole with a diameter of 250 μm in the right macular area, although the VA did not improve. Another 24-day observation showed that the MH diameter increased to 290 μm, and required surgical intervention. The surgical procedure included a standard three-channel vitrectomy, artificial posterior retinal detachment, fluid-air exchange, and SF6 gas filling without ILM peeling. The VA increased to 0.7 within 2 weeks. For this patient, MH was thought to derive from the

subclinical ILM or retinal microcracks from the shock wave of the laser, which were enlarged by the tension of the posterior vitreous membrane or ILM. It was the process of MH formation, mechanical enlargement of microcracks without any retinal cell defects that might account for the rapid recovery and good prognosis of VA.

In the current study the post-operative recovery of visual function of the four MH groups with different causes was influenced by different influencing factors.

In the IMH group, the factors influencing BCVA improvement in comparison with pre-operative VA included the following: 1. RD after the first MH-OP (7.118 [chi-square], P=0.018); RD was the complication after intra-ocular surgery which caused severe visual impairment; 2. cataract surgery (P=0.00); the affected eye undergoing cataract surgery had better post-operative BCVA; 3. total number of intra-ocular surgery after the initial MH-OP and the total number of intra-ocular surgery (Spearman rank correlation coefficient=0.180, P=0.002; Spearman rank correlation coefficient=0.1521, P=0.011); the statistical data indicated that the subsequent surgical treatment after MH-OP would not damage recovery of VA, while it was the necessary surgical treatment and facilitated the increase in BCVA; 4. pre-operative VA (Spearman rank correlation coefficient=-0.159, P=0.007); the better the pre-operative VA, the lower the improvement of post-operative BCVA; 5. post-operative visual field defect (P=0.000); and 6. cataract at the final follow-up (Spearman rank correlation coefficient=-0.306, P=0.001); the more severe the cataract, the worse the post-operative BCVA improvement.

The factors influencing post-operative final VA improvement were similar to the factors influencing post-operative BCVA, including RD after the first MH-OP (6.791 [chi-square], P=0.030), cataract surgery (P=0.001), total number of intra-ocular surgeries after the initial MH-OP (Spearman rank correlation coefficient 0.117, P=0.049), pre-operative VA (Spearman rank correlation coefficient -0.126，P=0.034), post-operative visual field defect (P=0.000), and cataracts at the final follow-up (Spearman rank correlation coefficient-0.237，P=0.001). In addition, RPE atrophy (9.864 [chi-square]， P=0.007) and optic disc paleness (P=0.022) also influenced the final VA improvement.

The basis for the post-operative decrease in final VA included ILM peeling or no ILM peeling (10.179 [chi-square], P=0.001). The incidence of a decreased final VA in comparison with BCVA of the affected eye reflected the following: ILM peeling was lower than no ILM peeling and intra-operative assistance with or without dye (10.129 [chi-square], P=0.001); the incidence of decrease in final VA in comparison with BCVA of the affected eye with intra-operative dye assistance was lower than without intra-operative dye assistance, but the increase in ICG concentration was a risk factor for decreased VA in comparison with BCVA (P=0.004, OR=0.717); the total number of MH-OP (P=0.005, OR=0.358); the re-occurrence of MH might impair VA of the affected eye; the more the MH-OP, the more severe the VA impairment; ILM rest after the first MH-OP (13.398 [chi-square], P=0.001); intra-operative ILM rest led to a higher MH re-occurrence ratio; RPE atrophy (11.889 [chi-square], P=0.003); and macular pigmentation (16.415 [chi-square], P=0.001) at the final follow-up were significantly correlated with the decrease in final VA.

In the IMH group, the abnormality of the Amsler grid and severity of centrocecal scotoma of the post-operative affected eye were correlated with the examination results of post-operative visual function. There was a negative correlation between the abnormality of the Amsler grid and severity of centrocecal scotoma and final VA improvement (Spearman rank correlation coefficient = -0.305 and -0.351, P=0.000), there was a negative correlation between the abnormality of the Amsler grid and severity of centrocecal scotoma and post-operative BCVA improvement (Spearman rank correlation coefficient = -0.343 and -0.299, P=0.000), and there was a correlation between the abnormality of the Amsler grid and severity of centrocecal scotoma and the decrease in final VA in comparison with BCVA (P=0.002, OR=0.659; P=0.002, OR=0.632).

In the HMMH group, among the study factors, we did not identify factors correlated with the decrease in post-operative final VA in comparison with BCVA after HMMH-OP; however, RD after the first MH-OP had a significant influence on post-operative BCVA and final VA improvement (6.210 [chi-square], P=0.045; 8.309 [chi-square], P=0.016). There was a negative correlation between the post-operative final VA improvement and

the total number of MH-OP (Spearman rank correlation coefficient = -0.339, P=0.043) and there was a correlation with intra-operative ILM rest (13.452 [chi-square], P=0.001). The abnormality of the Amsler grid at the final follow-up might reflect the decrease in post-operative final VA in comparison with BCVA (P=0.029, OR=0.265).

In the TMH group, the more the MH-OP, the worse the post-operative BCVA and final VA improvement in comparison with the pre-operative VA, and the two were negatively correlated (Spearman rank correlation coefficient = -0.650, P=0.012; Spearman rank correlation coefficient = -0.632, P=0.015). The severity of centrocecal scotoma at the final follow-up was negatively correlated with the post-operative BCVA improvement (P=0.013, Spearman rank correlation coefficient = 0.817).

In the SMH group, the pre-operative VA was negatively correlated with the post-operative BCVA and final VA improvement (Spearman rank correlation coefficient = -0.173, P=0.033; Spearman rank correlation coefficient = -0.171, P=0.035). The higher the ICG concentration, the better the post-operative BCVA (Spearman rank correlation coefficient = 0.204, P=0.048). RD after the first MH-OP had a significant effect on post-operative BCVA and final VA improvement (11.751 [chi-square], P=0.003; 6.843 [chi-square], P=0.024). The greater the number of intra-ocular surgeries after the initial MH-OP or the total number of intra-ocular surgeries, the higher the post-operative BCVA improvement (Spearman rank correlation coefficient = 0.236, P=0.003; Spearman rank correlation coefficient = 0.254, P=0.002). The Amsler grid at the final follow-up had a negative correlation with post-operative BCVA improvement (Spearman rank correlation coefficient = -0.262, P=0.004; Spearman rank correlation coefficient = -0.352, P=0.000). In this group, no factors were correlated with the decrease in final VA.

The factors influencing visual function recovery after MH-OP of the four groups are summarized, as follows: 1. RD after the first MH-OP had a significant influence on post-operative VA improvement (IMH, HMMH, and SMH groups). 2. The greater the number of MH-OP, the worse the VA recovery (IMH, HMMH, and SMH groups). 3. Intra-operative ILM rest had a negative influence on post-operative visual function recovery (IMH and HMMH groups). 4. The greater the pre-operative VA, the lower the

post-operative VA improvement (IMH and SMH groups). 5. Other intra-ocular surgeries did not increase the re-occurrence of MH, while the necessary surgical treatment might increase VA recovery (IMH and SMH groups), including cataract surgery. 6. Amsler grid examinations in the IMH, HMMH, and SMH groups and the centrocecal scotoma in the IMH and TMH groups had good synchrony in reflecting post-operative visual function status. These two examinations were feasible and low in cost.

Moreover, in the IMH group, changes in RPE at the final follow-up, including RPE atrophy and pigmentation, were negative factors for post-operative final VA impairment. RPE is composed of hexahedral cells in a regular monolayer. RPE cells become thicker in the macular area, but thinner at the periphery, as a pigment barrier with multiple biochemical functions supporting the activity of the photoreceptor, nourishing the outer retinal layer via the choroid, and phagocytosing exfoliated disk membranes and metabolites from the outer segment of the photoreceptor. RPE cells cannot regenerate after death so that the defects are covered by the shift of the neighboring pigment epithelial cells. Therefore, RPE cells have a direct impact on the function of the photoreceptor. As the macula is specialized for high acuity vision, macular RPE injury impairs the VA significantly. Kumagai et al.[221] analyzed the association between contributing factors with post-operative VA in two subsets of MH patients, including patients suffering from local macular retinal pigment epithelial loss and damage. The factors associated with post-operative VA are listed in order of diminishing importance: gender; age; baseline VA; stage of MH; onset of symptoms; size of the MH; and length of the ocular axis. In patients with RPE damage, the post-operative VA in eyes with lesions was associated with age and baseline acuity only, suggesting that the status of local macular RPE might be directly associated with the post-operative visual recovery. Patel et al.[222] reported that in contrast to general idiopathic MH, MH in highly myopic eyes had a worse post-operative closure rate and visual improvement. This study suggested that intact structure and function of local macular RPE and choroid is critical for post-operative visual recovery. The causes of pigment epithelial injuries include ICG toxicity, phototoxicity, direct damage from ILM peeling, and dynamic damage from the infusion of liquid. The sterile inflammation of previously injured cells from the

mechanical force of intra-operative vibration can also cause pigment epithelial damage, including pre-operative retinal laser photocoagulation, which causes direct damage to the RPE layer. Therefore, throughout the process of surgical treatment, any factor that may damage local macular RPE or choroid should be minimized.

5.5 Analysis of causes of post-operative MH recurrence and surgical failure

MHs are likely to recur post-operatively, most of which can heal after multiple surgeries. Kumagai et al.[228] reported that the recurrence of MH might be associated with the myopia of operated eyes and intra-operative retinal tears. ILM peeling significantly decreased the incidence of MH recurrence. The low incidence of recurrence after ILM peeling suggests that ILM was probably involved in MH recurrence.[186] Schumann et al.[29] reported that the incomplete posterior vitreous detachment rendered the occurrence of pre-macular membranes in MH patients. Several authors have reported the potentially causative relationship between the formation of the epiretinal membrane and the recurrence of MHs,[186, 229-231] and proposed that the contraction from the macular epiretinal membrane might be the cause of MH recurrence. Yoshida et al.[230] suggested that MHs can be attributed to the tangential contraction of ERM, whereas ILM peeling might reduce the risk of post-operative ERM, further decreasing the recurrence of MHs. In 161 MH eyes without ILM peeling and 150 eyes with ILM peeling, the post-operative recurrence of MHs showed that MHs were closed in 85% of eyes without ILM peeling and in 94% of eyes with ILM peeling at the initial surgery. The two subsets of patients were followed for 25 and 30 months, respectively. MHs recurred in 6 (4%) eyes without ILM peeling, and did not recur in any eye with ILM peeling. The first recurrence occurred 6-8 months following the initial surgery, and was associated with the formation of ERM at the periphery of the MH. The MH was closed in four eyes following the peeling of the pre-macular membrane and in two eyes following the peeling of the ILM. Kumagai et al.[228] reported that MHs recurred in 2 (0.39%) of 514 ILM-off eyes and in 26 (7.2%) of

363 ILM-on eyes, whereas no evident ERM was identified among the 28 recurrences.

In the IMH group, the better the pre-operative VA, the higher the success rate of the initial MH-OP (P=0.000, OR=1.350) and the higher the MH closure rate (P=0.008, OR=1.509). A good pre-operative VA was a protective factor for the success of MH-OP. An increase in the number of intra-ocular surgeries after the initial MH-OP did not cause re-occurrence of MHs (P=0.000, OR=7.606), and was a protective factor for the success of MH-OP. The intra-operative ILM rest increased the failure rate of MH-OP (5.284 [chi-square], P=0.040).

In the HMMH group, through an analysis of multiple factors, we found that the number of intra-ocular surgeries after the initial MH-OP and the total number of intra-ocular surgeries were protective factors for the success of MH-OP (P=0.045，OR=10.312), which was similar to the results in the IMH group. The increase in the number of intra-ocular surgeries after the initial MH-OP did not influence the re-occurrence of MH. The intra-operative ILM rest increased the re-occurrence of MH (7.404 [chi-square], P=0.015).

In the TMH group, multiple study factors, including operative details, pre- and post-operative status of affected eyes, and complications were not shown to be correlated with the success or failure of MH-OP.

In the SMH group, among the multiple study factors, the success or failure of MH-OP was only correlated with with or without intra-operative dye assistance (P=0.013). The success rate of dye-assisted MH-OP was higher than without dye assistance, while the operative details, pre- and post-operative status of the affected eyes, and complications were not shown to be correlated with the success or failure of MH-OP.

In the IMH and HMMH groups, ILM rest was closely correlated with the success or failure of MH-OP. The statistical results coincided with the clinical manifestations we observed; however, the observed cases in the HMMH group were limited to 36 eyes. Thus, the statistical data might be biased. We only adopted the data of the IMH group to analyze the possible correlation between the intra-operative ILM rest and post-operative ERM, suggesting that ILM peeling or no ILM peeling had no significant statistical difference in the occurrence of ERM (*P* = 0.258). Post-operative residual ILM

(including the entire ILM without ILM peeling) led to a higher occurrence of post-operative ERM (*P* = 0.000 and P=0.000, respectively). In the clinic, the treatment of MHs with difference causes also referred to the treatment experience in IMH. Through observations on the re-occurred MHs, we hypothesize that residual ILM and post-operative ERM had a critical effect on the success of MH surgery. Complete ILM peeling at the time of the initial MH surgery could significantly decrease the occurrence of macular ERM due to the stimulation of residual ILM, further minimizing the recurrence of MHs.

5.6 Surgical timing

Both patients and ophthalmologists prioritize the post-operative visual recovery following MH surgery. MHs with different causes may have some necessary factors influencing VA, such as highly myopic scleral staphyloma, trauma, or retinal detachment. Ophthalmologists have always sought to optimize visual recovery and the balance between visual damage and recovery. Additionally, how to minimize the occurrence of complications and recurrence is another factor in surgical planning. Apparently, not only determining surgical timing is critical, but all of the surgical details must be included. Gass et al.[17] proposed that management in the acute stages of MH was initially theorized to have the best potential for prevention of visual loss. OCT examinations were a breakthrough in the recognition of MH. Stage I MH is readily identifiable by OCT, thus the outcome emerges as an issue. The visual symptoms in stage I are mild and patients do not promptly seek medical attention. Those patients with spontaneous resolution may never require a clinical examination. Generally, stage I MH patients with a VA > 0.5 and can be followed up due to the slow progression of MH; however, it has been reported that the risk of progression of stage I MH increases as BCVA worsened (66% progression with 20/50 or worse vision).[232] Most cases of stage II MH have been reported to progress to stages III and IV, except for the few that remain at stage II or heal spontaneously. It has been reported that 40% of stage I MHs progress to full-thickness MH within 2 years; 85% of stage II MHs enlarge within 2

years, and 96% progress to stage III or IV; stage III and IV MHs remain stable or enlarge within 5 years, with VA decreasing to 0.1-0.05.[233] For the contralateral eyes in MH patients, there is a 15.6% risk of full-thickness MH within 5 years without posterior vitreous detachment, a risk < 2% in the presence of posterior vitreous detachment, or 40% within 1 year in the case of stage I MH.[234]

Since the first report of MH surgery in 1991, this procedure has been extensively used worldwide; however, the surgical timing remains controversial. Initially, due to the immaturity of surgical techniques and instruments, MH surgery was scheduled only at stage III and IV when patients had poor VA. The development and improvement in surgical techniques and instruments led to a surgical breakthrough in MH procedures that had been a challenge for > 2 decades. It remains unclear whether or not earlier surgery is likely to achieve better outcomes. For example, is it possible to rescue the VA before the onset of severe damage rather than simply achieving anatomic reduction? Anatomically, the macular inner retinal layer becomes progressively thinner, forming an oblique foveal bottom. The foveal retina is extremely thin (thickness = 0.132 nm), with an outer nuclear layer only, but without any other layers where only cone cells are present. Cone cells become thinner and longer with a large number and dense arrangement. At the fovea, each cone cell is connected to a bipolar cell only. The superiority of the fovea is due to the high and central VA. An oblique slope forms from the fovea to the periphery and the retina becomes progressively thicker, consisting of eccentric and peripheral areas. With the increase in the distance to the fovea, cone cells diminish in number and VA also decreases (i.e., paracentral or eccentric vision). With the development of MH, central scotoma and the Watzke test are able to indirectly reflect the defects in macular retinal tissue, indicating a variation in VA between various stages. Gass classified IMH into four stages, as follows: stage I (early MH) involving foveal detachment, with a VA of 0.3-0.8 as central vision; stages III and IV (full-thickness MH), with a VA of 0.05-0.3 as eccentric vision; and in stage II MH, crescent holes occurred at the foveal edges and progressed into circular full-thickness holes with central or eccentric vision. Kitaya et al.[235] reported that in 24 post-MH surgery patients, on OCT examination the presence of regular or irregular

photoreceptor layers in operated eyes was discriminated based on the presence of a regular line above the RPE layer. In 15 eyes with a VA ≥ 0.7, 12 eyes (80%) exhibited a regular photoreceptor layer; of 9 eyes with an acuity of <0.7, 6 (67%) exhibited an irregular photoreceptor layer. The authors proposed that the irregularity in the photoreceptor layers of operated eyes on OCT examination impaired the improvement of post-operative vision. Pre-operatively, of 12 MH eyes at stage II, 10 (83%) exhibited a regular photoreceptor layer on OCT examination, whereas of 11 MH eyes at stage III, 5 (45%) exhibited a regular layer. In MH eyee at stage IV (n = 1), OCT did not identify any photoreceptor layer. The irregular reflection of a photoreceptor layer indicated the destruction of this layer, resulting in the direct impairment of post-operative visual recovery. At the early stage of MH, the size of MH is small and the damage to the photoreceptor layer is mild, leading to a better visual prognosis if surgically treated. Kang et al.[236] reported similar results. Benson et al.[237] reviewed > 400 papers regarding MH surgery published between 1968 and 2000 to determine the optimal surgical timing for MH. Kang et al.[236] concluded that stage I MH was not indicated for surgical treatment, but MH surgery could block the progression of MH, which would damage VA. The VA of most stage III and IV MH patients improved post-operatively. Theses conclusions were based on the experience of previous decades. Our study indicated that although the poor pre-operative VA might have better VA improvement, better pre-operative VA might maintain better post-operative VA and ensure a higher success rate of MH-OP, which coincided with the results of previous studies.[238-240] MH stage had a different influence on VA and VA recovery of MH with difference causes. In the IMH group, the higher the MH stage, the worse the pre-operative VA, while there was no significant influence on the post-operative BCVA and final VA. In the TMH group, the correlation between VA and MH stage was not significant; however, in the HMMH and SMH groups, pre- and post-operative VA improvement had a significant correlation with MH stage. The higher the stage, the worse the VA. Thus, in combination with the aforementioned factors, as for I-II stage MH, when the visual function impairment was not severe, patients with IMH and TMH should be observed, while the patients with HMMH and SMH should undergo surgery as early as possible.

Our study also showed that MH surgery had a higher anatomic success rate than a functional recovery rate. The MH repair resulted in a significant improvement in the quality of vision and life for patients. Such improvement was also quite evident in patients with a contralateral normal near vision.[241]

There were significant limitations to this study. In this retrospective study, the observation targets and the period of follow-up were not uniform. In addition, there was no control group. The patients in the HMMH and TMH groups were insufficient, thus statistical bias was inevitable. The cases we collected were between 1993 and 2008. Because of the limitations of ophthalmologic examination instruments, some relevant examination indices were incomplete. For example, due to the popularization and updating of OCT equipment, MH became the routine examination item after 2004, although patients began to undergo this examination in 1994. Moreover, the image quality and definition on macular structure increased significantly over time. Not all patients had OCT examinations before and after surgery. Thus, we lacked data about MH size. The MH stage of some patients was judged by the naked eye, including the diagnosis of macular edema, ILM rest, and macular ERM. The examination of visual function was also not objective because there was no microperimetry or multifocal electroretinograms. In addition, the data about pre- and post-operative near vision, as well as the pre- and post-operative centrocecal scotoma changes were incomplete. The bias caused by the improvement in surgical instruments, equipment, and surgical skills was also inevitable.

In conclusion, the standard pars plana three-channel closed-type vitrectomy was shown to be effective for the treatment of MH with multiple causes in combination with ICG staining-assisted ILM peeling, infusion of autologous platelets into the MH, and SF6 vitreous filling. There are no data supporting intra-operative ILM peeling resulting in a higher success rate of MH-OP or VA improvement, but among the patients with IMH, the occurrence of decreased final VA in the ILM peeling group was low. ICG staining at a relatively low concentration was helpful with respect to the success rate of MH-OP and post-operative VA recovery. With a continuous improvement in surgical skills, successful and complete ILM peeling may not only effectively reduce the ERM

caused by ILM rest, which further reduces the reoccurrence rate of MH, but also alleviates the injury to ILM tissues and further reduces the influence on post-operative visual function recovery. Reducing the occurrence of post-operative retinal detachment has significant protection on post-operative VA improvement. Regarding stage I-II MH, when the visual function impairment was not severe, patients with IMH and TMH should be observed, while patients with HMMH and SMH should undergo surgery as early as possible. Synchronous or asynchronous cataract and MH surgeries had a minimal effect on the success of MH. Cataract surgery resulted in better visual improvement in operated eyes. Further studies on the minimization of procedural injuries and post-operative complications are in progress.

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Abbreviations	
AO	adaptive optics
BBG	brilliant blue G
BCVA	best corrected visual acuity
CME	cystoid macular edema
CNV	choroidal neovascularization
CNVM	choroidal neovascularization membrane
DM	diabetes mellitus
DR	diabetic retinopathy
ERGs	electroretinograms
ERM	epiretinal membrane
FAF	fundus autofluorescence
FDP	face-down position
fERG	focal electroretinogram
FFA	fundus fluorescein angiography
FGF	fibroblast growth factor
HBP	high blood pressure
HMMH	highly myopic macular hole
HRT	heidelberg retina tomograph
ICCE	intracapsular cataract extraction
ICG	indocyanine green
IFCG	infracyanine green

ILM	internal limiting membrane
ILM-peeling	internal limiting membrane-peeling
IMH	idiopathic macular hole
IOL	intraocular lens
IOP	intraocular pressure
LMH	lamellar macular hole
mfERG	multifocal electroretinogram
MH	macular hole
MPH	macular pseudohole
NPDR	none proliferating diabetic retinopathy
OCT	optical coherence tomography
PDGF	platelet-derived growth factor
PDR	proliferating diabetic retinopathy
PE	pigment epithelium
PFO	perfluoro-n-octane
Phaco	phaco-emulsification
Phaco+IOL	phaco-emulsification and intraocular lens implantation
PPV	pars plana vitrectomy
PPVD	perifoveal posterior vitreous detachment
PVD	posterior vitreous detachment
PVR	proliferative vitreous retinopathy

RD	retinal detachment
RPE	retinal pigment epithelium
RPEA	retinal pigment epithelium atrophy
RRD	rhegmatogenous retinal detachment
RTA	retinal thickness analyzer
SD-OCT	spectral domain optical coherence tomography
SLO	scanning laser ophthalmoscope
SMH	secondary macular hole
TA	triamcinolone acetonide
TB	trypan blue
TGF-β2	transforming growth factor-β2
UHR-OCT	ultrahigh-resolution optical coherence tomography
VA	visual acuity
20G	20-gauge
23G	23-gauge
25G	25-gauge
27G	27-gauge

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Curriculum Vitae

My resume/curriculum vitae is not published for privacy reasons in the electronic version of my work.

Publikationen

1. ZHANG Rijia，CUI Yubo, ZHANG Xu, et al. *Experimental research of salvia miltiorrhiza inhibiting retinal neovascularization in rats* [J]. Chin J Pract Ophthalmol, February. 2013, Vol 31, (2):234-238.

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6. Zhang Rijia, Chen Jian. *Ophthalmologic consulatation on diabetic patients* [J]. Clinical Focus, Nov. 2003, Vol 18(21):1218-1220.

[Component of the dissertation]

Affidavit

“I, [Rijia, Zhang] certify under penalty of perjury by my own signature that I have submitted the thesis on the topic [Functional Result of macular Hole Surgery (Funktionelle Ergebnisse nach Makulaforamenchirurgie)] I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date 2015-07-27 Signature Rijia Zhang

Declaration of any eventual publications

[Name of the doctoral candidates] had the following share in the following publications:

Publication 1: [Authors], [titles], [magazine], [year of publication]
Contribution in detail (please briefly explain):

Publication 2: [Authors], [titles], [magazine], [year of publication]
Contribution in detail (please briefly explain):

Publication 3: [Authors], [titles], [magazine], [year of publication]
Contribution in detail (please briefly explain):

Signature, date and stamp of the supervising University teacher

_____

Signature of the doctoral candidate

_____Rijia Zhang_____