• Meta-Analysis •

Vitrectomy with internal limiting membrane peeling versus its flap insertion for macular hole in high myopia: a Meta-analysis

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Abstract

● **AIM:** To compare the anatomic and functional outcomes between vitrectomy with internal limiting membrane (ILM) peeling and internal ILM flap insertion technique for high myopia macular hole (MH).

● **METHODS:** PubMed, Cochrane Library, EMBASE, and CNKI were systematically searched, and all studies involved MH were included. The closure rate of MH and the postoperative best-corrected visual acuity (BCVA) at 6mo after the initial surgery were the primary measures. All statistical tests were performed in Review Manager 5.3.

● **RESULTS:** Five studies that included 151 eyes of 151 patients were finally included, all of which were retrospectively comparative studies. Between the pars plana vitrectomy (PPV) with ILM peeling surgery and the ILM insertion technique, the latter had significantly better efficacy with respect to the closure rate of MH (OR=21.32, 95%CI=7.25-62.67, *P*<0.001); However, regarding BCVA at 6mo after the initial surgery in MH, there was no statistical significance between the groups (OR=-0.04, 95%CI=-0.22-0.14, *P*=0.66). In addition, regarding the rate of retinal reattachment after the initial surgery, the two different methods were not significantly different (OR=2.22, 95%CI=0.34-14.32, *P*=0.4).

● **CONCLUSION:** Both ILM peeling and ILM insertion technique could significantly improve anatomic outcomes of MH in high myopia with or without retinal detachment (RD), and anatomic outcomes are more effective. However, there is no statistical significance in BCVA at 6mo after the initial surgery in MH, or in the rate of retinal reattachment after the first surgery, between the two methods.

● **KEYWORDS:** macular hole; high myopia; best-corrected visual acuity; retinal attachment; Meta-analysis

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INTRODUCTION

Macular hole (MH) is a full-thickness neuroretinal defect that occurs in the retina. According to the International Vitreomacular Traction Study (IVTS), vitreous liquefaction will lead to posterior vitreous detachment and further progress to vitreous macular adhesion, which can eventually develop into pathological vitreous macular traction and MH, the latter usually will result in the damage to central vision. High myopia MH [axial length >26 mm or diopter (D) of at least 6[1]] is one of the most common types of MH, which can easily lead to retinal detachment (RD)[2-3].

Vitrectomy with traditional internal limiting membrane (ILM) peeling technique is regarded as the gold standard treatment for MH; it works by completely relieving of the traction of the macula and increasing the flexibility of the retina[4]. However, the ILM peeling technique may fail to close the hole, or may cause secondary MH or foveoschisis[5-6]. Recently, an ILM insertion technique was developed; it has steadily grown in popularity as a modified method for treatment of high myopia MH. In fact, there are several different inverted ILM flap techniques, among them. Free ILM flap and inverted ILM flaps are most commonly used in the surgery. Morizane *et al*[7] first reported the ILM insertion technique; they transplanted the free

ILM to fill the hole, and confirmed that the insertion technique was an effective approach for persistent refractory MHs, including in patients with high myopia MHs that did not close after conventional ILM peeling approach. In order to improve the cure rate of MH, Chen and Yang[8] attempted to peel part of the ILM along the edge of the hole, taking care not to remove it completely, and then inverted the ILM and inserted it into the hole. Eventually they confirmed that compared to ILM peeling alone, the inverted ILM insertion technique could help improve the rate of closure of high myopia MHs.

However, there have not been large numbers of investigations to distinguish the outcomes such as the MH closure rate between conventional pars plana vitrectomy (PPV) combined with ILM peeling and PPV combined with ILM insertion into the MH. Thus, in order to determine which approach has better anatomic and functional outcomes after the initial operation, we performed a Meta-analysis to compare these two methods for the treatment of high myopia MH. We assessed MH closure rate and best-corrected visual acuity (BCVA) at 6mo after the initial surgery, as well as the rate of retinal reattachment in patients with high myopia MH combined with RD.

MATERIALS AND METHODS

This Meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy In this Meta-analysis, all relevant studies were hunted from PubMed, Cochrane Library, Embase and CKNI (the largest database of science in China). We were searching the studies by using following terms: “macular hole” OR “retinal break” AND “high myopia” AND “internal limiting membrane peeling” OR “ILM flap insertion”. Final search was carried out on June 2018. There were no restrictions in included articles’ language and publishing year. Studies with available dates were included. Review, case report, meeting abstract and articles lacks comparing were excluded.

Criteria For Inclusion and Exclusion

Data inclusion The considering studies should fulfill following criteria: 1) comparing outcomes of patients treated with vitrectomy with conventional ILM peeling *vs* ILM flap insertion for MH in high myopia; 2) retrospective study reported the surgery treatment for MH in high myopia; 3) reporting the detailed and sufficient outcomes, such as the rate of MH closure and BCVA, and following-up’s data.

By reading titles and abstracts, two independent investigators (Yan L and Wu N) roughly selected useful articles, also they read the full texts to choose those potential literatures in the Meta-analysis, which following above criteria.

Data extraction Two reviewers extracted information from included studies independently and rechecked carefully. Any disagreement regarding eligibility during the extraction was discussed by the two reviewers and had been resolved. The data from selected studies included the first author, publication year, country, trial type, age, gender, axial length number of subjects, surgical procedures, gas used, closure rate preoperative and postoperative BCVA. The exclusive criteria as follows: 1) the study was designed “as reviews but without primary outcomes” or “case reports” or “meeting abstracts”; 2) the study was prospective multicenter randomized controlled trial (RCT); 3) the research objects were animals rather than human; 4) the operative date was poor or unavailable in the literatures. In order to get high-quality studies, two independent reviewers participated in excluding articles following above criteria.

Statistical Analysis Cochrane Collaboration’s Review Manager Software (RevMan Version 5.3, Cochrane Community) was used for data analysis. We analyzed dichotomous variables: the closure rate of MH by using estimation of odds ratios (OR) with a 95% confidence interval (CI). For continuous outcome data like BCVA, we converted these data to the mean and standard deviation by using the method reported by Hozo *et al*[9]. Statistical heterogeneity among studies was evaluated with the Q test and I^2 statistic, and $P<0.1$ and $I^2>50\%$ indicating significant heterogeneity. If $P<0.1$ and $I^2>50\%$, a random-effects model was used for the Meta-analysis; otherwise, the fixed-effect model was used. Publication bias was evaluated by using a funnel plot.

RESULTS

Selection of Studies In total, 1052 articles were initially identified; 1003 of these were identified in database searches, while 49 records were found through other sources. After removal of duplicate records, 670 studies were retained; following application of the inclusion and exclusion criteria, 5 articles, which were all retrospective studies, were used in this analysis[8,10-13]. The process is illustrated in greater detail in the flow diagram of Figure 1.

Characteristics and Baseline of the Included Studies This Meta-analysis included 5 studies, which involved 151 eyes; 62 eyes underwent ILM flap insertion, while 89 eyes underwent conventional ILM peeling. The characteristics of these eyes are listed in Table 1, including age, sex, presence or absence of RD, and axial length. Intraoperative staining of the ILM was performed by indocyanine green (ICG), brilliant blue G (BBG) or triamcinolone acetonide (TA); gas tamponade involving sulfur hexafluoride (SF_6) or perfluoropropane (C_3F_8), and silicone oil (SO) was used after ILM peeling.

All studies were retrospective analyses; two were performed in Japan, three in Taiwan, China (Table 1). Table 2 depicts the quality of studies included in this Meta-analysis; total scores ranged from 14 to 18, generally speaking, the quality of researches were moderate to good.

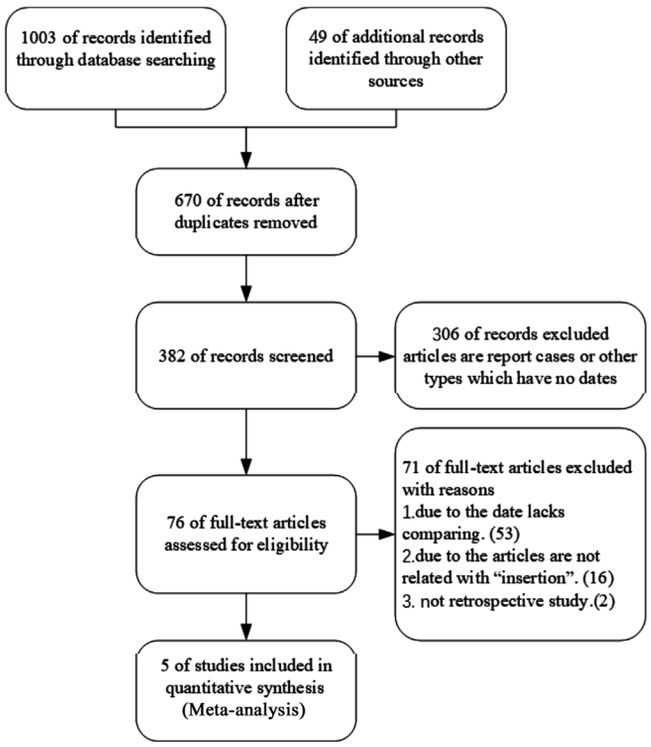

Figure 1 Flow diagram of the literature search strategy.

Outcomes of the Meta-analysis Figure 2 shows forest plots comparing the results of the ILM insertion group with those of the ILM peeling group; the rate of closure of MH in the ILM insertion group was significantly better than that of the ILM peeling group in all studies (OR=21.32, 95%CI=7.25-62.67, P<0.001, Figure 2A), with no heterogeneity (I^2=0, P=0.73, Figure 2A). In the subgroup Meta-analysis of patients with MH combined with RD, 4 studies were finally included; there was no significant difference in the rate of retinal reattachment of the MH between the ILM insertion and ILM peeling groups (OR=2.22, 95%CI=0.34-14.32, P=0.4, Figure 2B); no heterogeneity was detected (I^2=0, P=0.83, Figure 2B). In order to determine which method could more clearly improve BCVA, we constructed two subgroups, preoperative BCVA and postoperative BCVA (6mo after the initial surgery); we used these groups to compare the effect between the conventional surgery and the insertion technique. The Figure 2 shows that preoperative BCVA was recorded in all 5 studies; there was no statistically significant difference between the techniques (OR=0.07, 95%CI=-0.09-0.22, P=0.4, Figure 2C). The postoperative BCVA also showed no significant difference between the ILM insertion and ILM peeling groups (OR=-0.04, 95%CI=-0.22-0.14, P=0.66, Figure 2D); both subgroups exhibited heterogeneity (preoperative group, I^2=11%, P=0.34, Figure 2C; postoperative group, I^2=54%, P=0.07, Figure 2D). Because the postoperative group showed high heterogeneity (I^2>50%), a random model was used.

Additionally, in the subgroup of MH combined with RD, due to the cumulative effect, two articles were excluded by Review

Table 1 Characteristics of the included studies

Study, year	Country	Study type	Groups	No. of eyes	Female/male	Retinal detachment	Area of RD within/beyond arcade	Age (y)	Axial length (mm)	Dye of ILM stained	Tamponade agents
Chen *et al*[8], 2016	Taiwan, China	Retro	Inverted ILM insertion	20	16/4	20	11/9	62.06±8.90	28.40±1.94	ICG (20)	C_3F_8
			ILM peeling	20	14/6	20	10/10	60.53±8.78	29.35±1.88	ICG (20)	C_3F_8
Baba *et al*[10], 2017	Japan	Retro	Inverted ILM insertion	10	5/5	10	6/4	73.00±96.67	28.98±1.31	BBG (10)	C_3F_8
			ILM peeling	11	8/3	11	7/4	69.75±91.70	30.17±1.68	BBG (11)	C_3F_8
Wu *et al*[11], 2017	Taiwan, China	Retro	Inverted ILM insertion	6	3/3	0	-	62.33±4.18	31.02±0.81	ICG (6)	C_3F_8
			ILM peeling	8	6/2	0	-	57.88±12.58	30.45±0.67	ICG (8)	C_3F_8
Wakabayashi *et al*[12], 2018	Japan	Retro	Inverted ILM insertion	13	11/2	13	5/8	67.80±9.90	29.40±0.90	BBG (10)/ICG (1)/TA (2)	SF_6 (10)/C_3F_8 (1)/SO (2)
			ILM peeling	36	34/2	36	7/29	69.20±9.10	29.60±1.50	BBG (19)/ICG (10)/TA (7)	SF_6 (10)/C_3F_8 (24)/SO (2)
Chen *et al*[13], 2018	Taiwan, China	Retro	Free ILM flap insertion	13	5/8	13	10/3	65.5±7.7	29.75±2.21	ICG (13)	SF_6/C_3F_8
			ILM peeling	14	5/9	14	12/2	62.4±8.6	29.45±1.58	ICG (14)	SF_6/C_3F_8

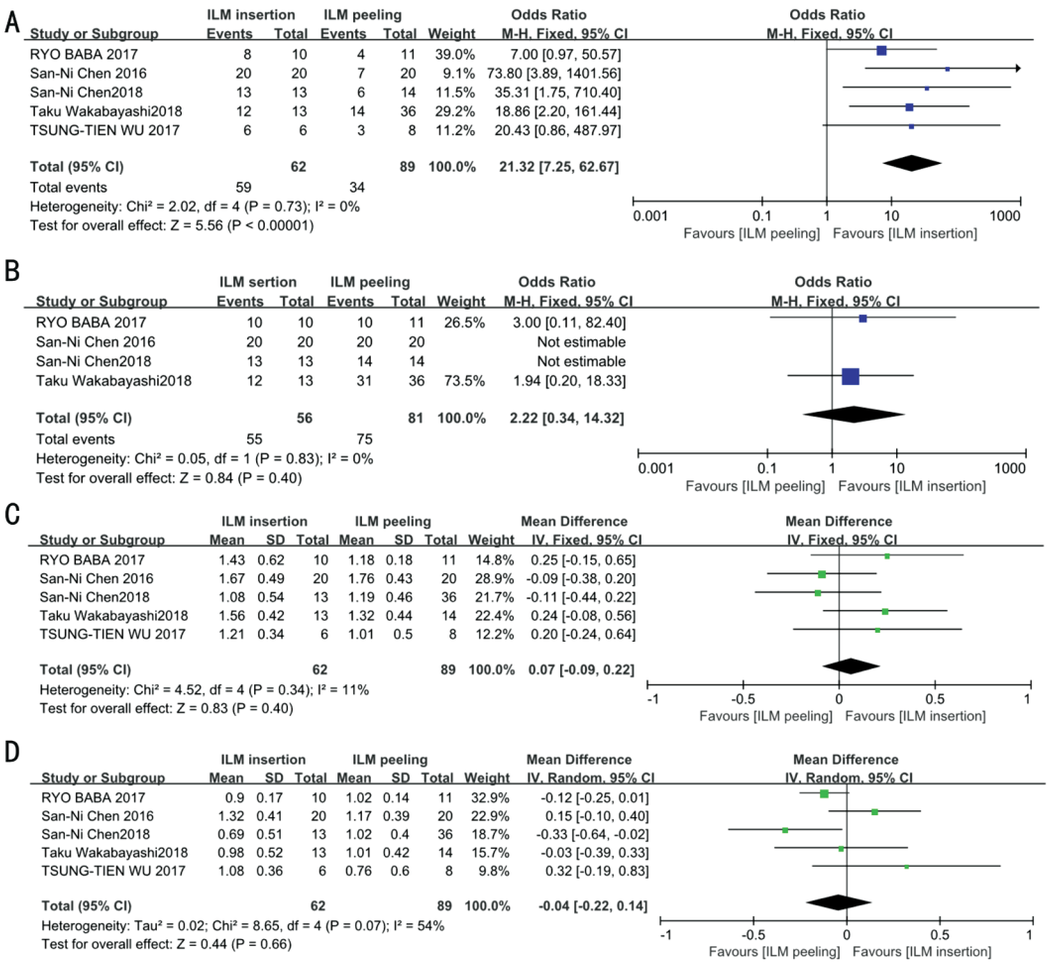

Figure 2 Forest plots of anatomic and functional outcomes of MH in high myopia after the first surgery A: The closure rate of MH of the all 5 studies; B: The retinal reattachment of MH of patients with RD; C: Preoperative BCVA of the all 5 studies; D: Postoperative BCVA later 6mo after the first surgery.

Table 2 MINORS for assessing quality of included studies

Methodological item for non-randomized studies	Chen *et al*[8], 2016	Baba *et al*[10], 2017	Wu *et al*[11], 2017	Wakabayashi *et al*[12], 2018	Chen *et al*[13], 2018
1. A clearly stated aim	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2
3. Prospective collection of data	2	0	1	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	0	2
7. Loss to follow up less than 5%	2	2	2	2	2
8. Prospective calculation of the study size	0	0	0	0	0
9. An adequate control group	2	2	2	2	2
10. Contemporary groups	0	0	0	0	0
11. Baseline equivalence of groups	2	2	2	0	2
12. Adequate statistical analyses	2	2	2	2	2
Total score	18	16	17	14	18

manager 5.3[8,13]; their rates of retinal reattachment in MH were 100% in both the ILM insertion and ILM peeling groups, such that ORs could not be calculated.

Testing for Publication Bias Figure 3 shows all four funnel plots for the closure rate, preoperative and postoperative BCVA, and retinal reattachment; none of these data exhibited obvious asymmetries, indicating that there was no serious publication bias in the included studies.

DISCUSSION

In this Meta-analysis, we included 5 studies that all compared

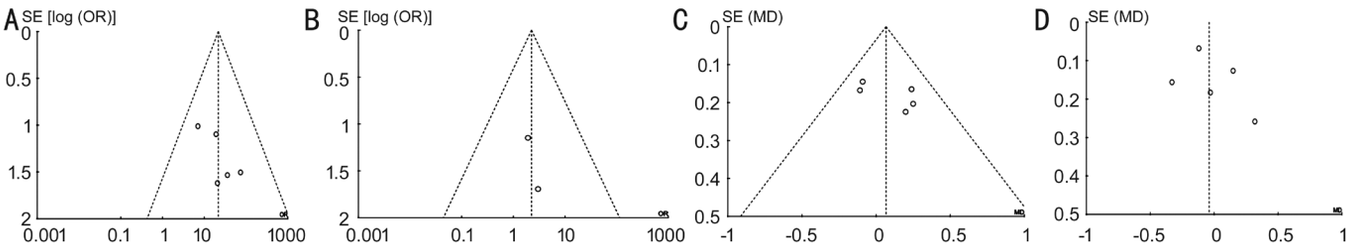

Figure 3 Funnel plots of literatures included in this Meta-analysis A: The closure rate of MH of the all 5 studies; B: The retinal reattachment of MH of patients with RD; C: Preoperative BCVA of the all 5 studies; D: Postoperative BCVA later 6mo after the first surgery.

the effects of the methods for surgical treatment of high myopia MH between the conventional ILM peeling technique and the modified ILM insertion technique. In total, 151 eyes of 151 patients were evaluated regarding the postoperative closure rate of the hole, which is the most critical ophthalmic examination result; moreover, we evaluated the preoperative and postoperative BCVA (6mo after the initial surgery). Additionally, we performed subgroup analysis regarding the rate of retinal reattachment after the initial surgery, among patients who exhibited MH combined with RD, which included the data from 4 studies. Many studies of ILM insertion have reported[8,10-13] that the ILM insertion technique could improve the closure rate, compared with that of conventional PPV with ILM peeling. In cases where the hole remained open after the initial operation, surgeons could choose to use the ILM flap to fill the hole; for treatment of recurrent and chronic patients, this modified technique could help to close the hole and to improve visual function[14]. In our study, the forest plot revealed that the insertion technique was better (P<0.05). However, regarding the rate of retinal reattachment after the initial surgery and the postoperative BCVA, there were no significant differences (P>0.05); the subgroup with high myopia MH with RD, a small amount of eyes were included, which may have led to the results of the forest plot (P>0.05).

Kelly and Wendel[15] first reported operative treatment for MH, which comprised PPV. Before that report, MH was considered incurable; Yooh *et al*[16] then demonstrated that ILM peeling combined with PPV was more effective for treatment of MH. Recently, this surgical method has been used for high myopia MH, with or without RD[17-19]. The surgical procedures have become standardized; thus, after the completion of PPV, experienced surgeons would use dye to identify the ILM, which was then peeled carefully in a circular manner around the hole by use of an ILM forceps, and completely removed from the retina. After fluid-gas exchange (injection of perfluoropropane gas tamponade or other gas into the vitreous cavity), patients were instructed to remain in the face-down position for approximately 2wk postoperatively; then, ophthalmic examination results were checked. Studies have shown a good anatomic outcome using simple MH; the approximate postoperative closure rate could reach 88%[20-21]; despite this considerable success in closure rate, an unavoidable failing rate could not be ignored, such that the hole may continue opening after operation. Additionally, for patients with MH combined with RD, the closure rate varied from 10%-70%[22]. Importantly, the ILM peeling approach often led to poor functional outcomes, especially with regard to postoperative visual outcomes[23-24]; some complications, such as outer retinal cysts, appeared after surgery because of leaking tissue in the subfoveal area[23].

In order to resolve patients' frustrations, reduce complications, and improve the success rate of the operations, many operators attempted to modify surgical processes, which were based on the traditional standard surgery method. In 2010, Michalewska *et al*[25] first reported the inverted ILM technique; they speculated that this modified technique could improve both anatomic and functional outcomes. The process of PPV was identical to that of the conventional technique. With respect to the ILM, Michalewska *et al*[25] peeled it around the hole for approximately 2 disc diameters; then, instead of completely removing the peeled ILM, they maintained a few fringes of ILM that were attached to the edge of the hole. In the next step, the ILM was inverted sufficiently to cover the surface of the hole; in this manner, glial cells might proliferate and then fill in the hole, resulting in ultimate closure of the hole. Furthermore, the ILM insertion technique was also a modified technique, similar to the classic inverted method; the primary difference was the processing procedure used for the ILM, such that the ILM was used to fill the hole, rather than to cover it. The Japanese ophthalmologists, Chen *et al*[8,13] performed multiple investigations of the insertion technique; in another study, they used the free ILM flap to treat chronic and persistent MH. After some effective surgeries, they found that, in patients who had MH combined with RD, the insertion technique had a higher closure rate than the conventional ILM peeling technique; moreover, insertion of double ILM could fix it well into the hole. Furthermore, many other ophthalmologists used the inverted ILM flap to fill and close the hole[6,21,26-28]. However, the submacular retinal pigment epithelium (RPE) exhibited atrophy 1wk after insertion of the ILM flap into the hole. Imai

and Azumi[26] speculated that the insertion technique may cause this condition. Fortunately, Chen and Yang[8] determined that the dye agent, ICG, was the source of the atrophy; clinicians should rinse away the ICG as soon as possible, because the toxicity of ICG may cause RPE atrophy. In contrast, change other safe one like BBG was better.

Notably, simply covering the surface of hole with ILM was worse than filling it[29], especially when the hole was particularly large or persisted postoperatively. Many studies have reported that the insertion technique has better anatomic and functional outcomes[13,30]. According to the study by Park *et al*[29] in some complex types of MH, such as big MH and high myopia MH, the insertion technique showed better recovery of the photoreceptor layers, compared with the classic inverted technique; moreover, the insertion technique also exhibited better visual outcome after surgery. Baba *et al*[10] believed that keeping the glial cells in the hole during surgery may facilitate the closure of the hole for high myopia MH. Rossi *et al*[31] investigated speculated that using the ILM flap to fill the hole could improve the closure rate more effectively than the classic inverted technique.

Importantly, the insertion technique has some advantages that are absent from the inverted covering technique. Previously, there was a Meta-analysis comparing the conventional peeling technique with the inverted technique by Yuan *et al*[32]; they showed that the inverted technique had a better effect on the closure rate at 6mo after the initial surgery, compared with the conventional technique; however, it did not result in better visual outcomes. The current insertion technique has thus far lacked a systematic comparison with the conventional gold standard technique. Yet, some interesting literatures have filled this gap. Currently, the ILM, which is used to fill the hole, has two types of ILM insertion technique, free ILM flap or inverted ILM flap. Of course, the latter approach was modified on the basis of the inverted covering technique. Zheng *et al*[33] randomly distributed 38 patients with high myopia MH into two groups; group 1 used the conventional PPV with ILM peeling technique, group 2 used the inverted ILM insertion technique. They found that the patients in group 2 had fewer complications and a better closure rate at 3mo after the initial surgery. Moreover, the insertion technique was concluded to be more effective and safer. Chen *et al*[13] used the free ILM flap, inserted into the hole of high myopia MH patients; after the operations, they found that this new technique had a higher closure rate than ILM peeling. However, in a recent study, Velez-Montoya *et al*[34] also used free ILM flap to fill the hole, and compared their findings with the postoperative effect of conventional ILM peeling. Notably, regarding the postoperative closure rate, that of the free flap technique was approximately 85% less than that of the conventional ILM peeling technique (91%); they speculated that the small number of patients may have contributed to this unusual finding.

In order to eliminate disputes, in this Meta-analysis, we searched studies comparing the ILM peeling and ILM insertion techniques. We systematically compared the anatomic and functional outcomes between these two techniques for patients with high myopia MH after the initial surgery, in order to ensure that this new modified technique would improve both anatomic and functional outcomes. We found 5 studies that concluded the ILM insertion technique could improve both closure rate and visual condition; among these 5 studies, 4[8,10,12-13] included patients with RD, and showed that the rate of retinal reattachment was higher when using the insertion technique. After statistical analysis, we concluded that the insertion technique was the better choice, as it can provide a higher closure rate; however, the postoperative BCVA at 6mo after surgery was not statistically different between the two methods. We suspect that this may be due to the small number of patients. The deficiencies in our study were the limited data available to analyze retinal reattachment between the two groups. Notably, of the 4 studies that included patients with high myopia MH combined with RD, the patients all exhibited retinal reattachment after surgery in ILM peeling and ILM insertion technique; we could not find a statistical difference between the two groups.

These results are representative and rigorous; surgeons may consider that, for patients with high myopia MH, the ILM insertion technique is a better method for hole closure.

The ILM insertion technique had better anatomical outcome with regard to closure rate for patients with high myopia MH, with or without RD; however, functional outcomes, such as BCVA or retinal reattachment, were similar to those of traditional ILM peeling. Additional studies with more patients may be needed to confirm these findings.

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