



RESEARCH ARTICLE

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## Inverted Internal Limiting Membrane Flap vs. ILM Peeling for <400 μm Macular Hole: A Meta-Analysis and Systematic Review

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### ABSTRACT

Inverted Internal Limiting Membrane (ILM) flap technique was developed to achieve Macular Hole (MH) closure in large MH. But the efficacy of small holes has been controversial. The aim of this study was to compare the anatomical and visual outcomes of vitrectomy (PPV) combined with the inverted ILM flap and ILM peeling in small and medium size MHs. Search relevant literature within PubMed, Web of Science, Embase, Cochrane library, and CNKI from inception through October 2022 in English or Chinese. Only case-control studies were included. Heterogeneity, publication bias, and sensitivity analysis were conducted to ensure the statistical power. This meta-analysis included six studies involving 299 eyes, 3 randomized control trials, and 3 retrospective studies. Summarizing data displayed that the MH closure rate was not different between the inverted ILM flap group and peeling group (Odds Ratio (OR) =0.29, 95% Confidence Interval (CI): 0.04 ~ 1.96, P=0.33). Whereas there was no significant difference in visual acuity improvement, the integrity of the External Limiting Membrane (ELM) and the Ellipsoid Zone (EZ) in 3 months or 12 months after surgery between the two groups. Therefore inverted ILM flap and ILM peeling are both effective treatments for <400 μm MHs, and are associated with comparable outcomes as well as don't damage the integrity of the retina.

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### KEYWORDS

Macular hole; Eye; Retina; Surgery

## Introduction

Macular Hole (MH) refers to the tissue defect from the inner limiting membrane of the retina to the photoreceptor layer in the macula area. Meanwhile, many patients feel severe visual decline, visual deformation, central scotoma, and other visual impairment. In 1988, Gass [1] suggested that the hole was the tensile force of a tangent line to the surface of the retina. To accelerate the holes close, the traction in the macular area needs to be relieved. Since Kelly, et al. [2] first reported the treatment of MH with ILM peeling in 1991, the rate of MH closure has been greatly improved. Therefore, PPV combined with ILM peeling, gas-liquid exchange during the surgery, and filled vitrectomy became the standard operation for MH [3-6].

The International Vitreomacular Traction Study Group categorized MH according to the size of the minimal diameter of the MH as follows: Small ( $\leq 250 \mu\text{m}$ ), medium (251–400  $\mu\text{m}$ ), and large ( $>400 \mu\text{m}$ ) [7]. Michalewska, et al. [8] introduced the ILM flap technique to treat large Full-Thickness Macular Holes (FTMH), which refined the standard ILM peeling, and the rate of hole closure arrived at 76%, only 52% in

traditional ILM peeling. Mahalingam, et al. [9] also reported that patients of large MH gain better visual acuity in the end by the ILM flap technique. This technique was beneficial for anatomic and functional outcomes for large, traumatic, myopic, and chronic FTMH, since then, more and more surgeons are willing to choose this way. However, it has long been debated whether the ILM flap is effective for small and medium size macular holes. Some studies thought traditional ILM peeling had achieved a very high closing rate, and inverted ILM flap made it harder to operate. But some new research showed that the inverted ILM flap achieved the same visual outcomes as ILM peeling, it resulted in faster visual acuity improvement and anatomical recovery in the early period [10-12].

In this meta-analysis, we comprehensively and quantitatively compared PPV with inverted ILM flap and ILM peeling in small and medium size MHs, to explore the optimal surgical approach for the treatment of <400 $\mu\text{m}$  MHs.

## Methods

### Search strategy

We cautiously searched for studies that used the in-

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verted ILM flap technique or ILM peeling to treat small and medium size MHs. The PubMed, Web of Science, Embase, Cochrane library, and CNKI databases were systematically searched for all articles including relevant prospective and retrospective clinical trials published before October 2022. The search terms “macular hole OR MH OR macular break” AND “inverted internal limiting membrane flap technique” OR “inverted ILM flap technique” AND “internal limiting membrane peeling” OR “ILM peeling” OR “internal limiting membrane removal” OR “removing the ILM” OR “ILM peel” were searched. To avoid literature omission, we also searched manually.

### Inclusion and exclusion criteria

According to the participants, intervention measures, comparison, results, and study design (PICOS) protocol, we used the following criteria: (I) Participants: diagnosed with MH and a minimum diameter of the hole <400  $\mu\text{m}$ ; (II) Intervention measures: the experimental group: participants chose PPV combined with inverted ILM flap, the control group: participants chose PPV combined with ILM peeling; (III) Outcome measures: including the effective rate of MH closure, preoperative and postoperative Best Corrected Visual Acuity (BCVA), postoperative ELM and EZ assessment results; (IV) Study design: Prospective randomized controlled trials, retrospective case trials.

The exclusion criteria were as follows: (I) Combination with severe cataract, glaucoma, myopia, retinal detachment, and other eye diseases. (II) Didn't provide the data required for this meta-analysis; (III) Follow-up time of fewer than 3 months; (IV) Poor quality of literature, missing data, duplicate reports; (V) Reviews or case reports.

### Data extraction

Data extraction was independently performed by two investigators, and any discrepancy between the extraction was resolved by discussion or consultation with a third researcher. Data extraction content included: first author, publication year, country, BCVA, follow-up time, and so on.

### Quality of assessment

The Randomized Control Trials (RCTs) were evaluated for quality by the “Risk of bias” tool recommended by the Cochrane Handbook 5.1.0. Studies were assessed on seven accepts: “random sequence generation,” “allocation concealment,” “blinding of participants and personnel,” “blinding of outcome assessment,” “incomplete outcome data,” “selective reporting,” and “other bias.” The methodological quality of retrospective case series was assessed based on the Newcastle-Ottawa Scale (NOS). Studies were rated in three areas: selection, comparability, and exposure. Scores  $\geq 6$  indicated

that the quality of research was relatively high.

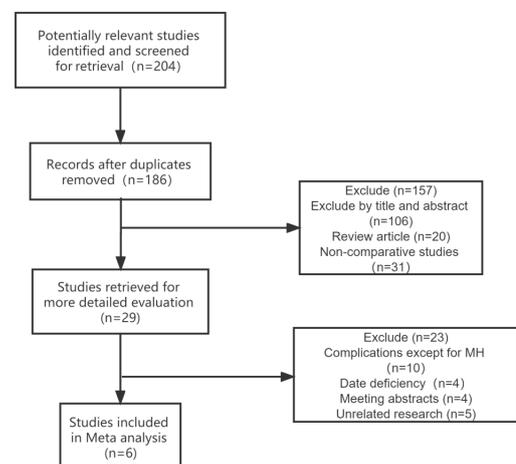
### Statistical analysis

Statistical analysis was performed using Review Manager 5.3 software. Cochrane test and I2 statistics were used to assess the heterogeneity of included studies. Values  $\geq 50\%$  indicated high heterogeneity, values between 25% and 50% indicated moderate heterogeneity, values between 0% and 25% indicated mild heterogeneity, and  $I^2=0\%$  indicates no heterogeneity [13]. When  $I^2 > 50\%$ , a random-effects model was used for data synthesis in the presence of significant heterogeneity, while a fixed-effects model was used when there was no significant heterogeneity. Dichotomous variable data results were stated as Odds Ratio (OR) with a 95% Confidence Interval (CI), while numerical variable data outcomes were recorded as Standardized Mean Difference (SMD) and a 95% CI. Differences were considered statistically significant at  $P < 0.05$ . Sensitivity analysis was used to verify whether the conclusion of the meta-analysis was robust and credible. Forest diagrams were applied to analyze the results of meta-analysis and funnel plots were applied to evaluate if the results had potential publication bias [14].

## Results

### Search results

The included literature processed in this meta-analysis is shown in Figure 1. Initially, a total of 204 studies were retrieved. After excluding 175 records by screening the titles and abstracts, a total of 29 articles were considered for more detailed evaluation. We ultimately included 6 studies [15-19] (299 eyes) in our meta-analysis, including 161 eyes in the ILM peeling group and 138 eyes in the inverted ILM flap group. Of these studies, 3 studies [19-21] were retrospective observational studies and 3 studies [16-18] were RCTs. The main characteristics of the included studies were listed in Table 1.



**Figure 1.** Flow diagram of the study selection process.

**Table 1.** Characteristics of the studies included in this meta-analysis.

Study	Year	Country	Group	Trial type	No. of eye	Age	Mean diameter of MH(µm)	Pre-BCVA, logMAR	Post-BCVA, logMAR	Follow up (months)
Luca Ventre [16]	2022	Italy	ILM flap	A randomized control trial	25	62	269	0.76	0.22	1, 3, 6, 12
			ILM peeling		25	64	254	0.72	0.19	1, 3, 6, 12
Christoph Leisser [17]	2022	Austria	ILM flap	A randomized control trial	7	71	275	NA	NA	3
			ILM peeling		9	67	244	NA	NA	3
Chang Su [18]	2018	China	ILM flap	A randomized control trial	15	48.7	<400	1.2	0.41	1, 3, 6
			ILM peeling		15	48.7	<400	1.34	0.45	1, 3, 6
Hung-Da Chou [19]	2021	China	ILM flap	A retrospective case trial	55	NA	261.6	1.05	0.48	1, 3, 6, 12
			ILM peeling		62	NA	251.9	1.05	0.51	1, 3, 6, 12
Carmen Baumann [20]	2021	Germany	ILM flap	A retrospective case trial	24	63.1	282	0.77	0.18	3, 6, 12
			ILM peeling		36	70.5	238	0.74	0.26	3, 6, 12
Kana-ko Yamada [21]	2022	Japan	ILM flap	A retrospective case trial	21	66.2	278.6	0.71	0.28	1, 3, 6, 12
			ILM peeling		21	66.6	276	0.73	0.24	1, 3, 6, 12

**Meta-analysis results**

**The rate of macular hole closure:** Five studies [16-19, 21] reported the MH closure rate after being treated with ILM peeling or inverted ILM flap. It was 97.3% (111/114 eyes) in the inverted ILM flap group and 99.2% (124/125 eyes) in the ILM peeling group. Due to  $I^2=0\%$ , we chose the fixed-effects model, the analysis showed that the MH closure rate wasn't significantly different between the two groups (OR=0.29, 95%CI: 0.04~1.96, P=0.33, Figure 2)

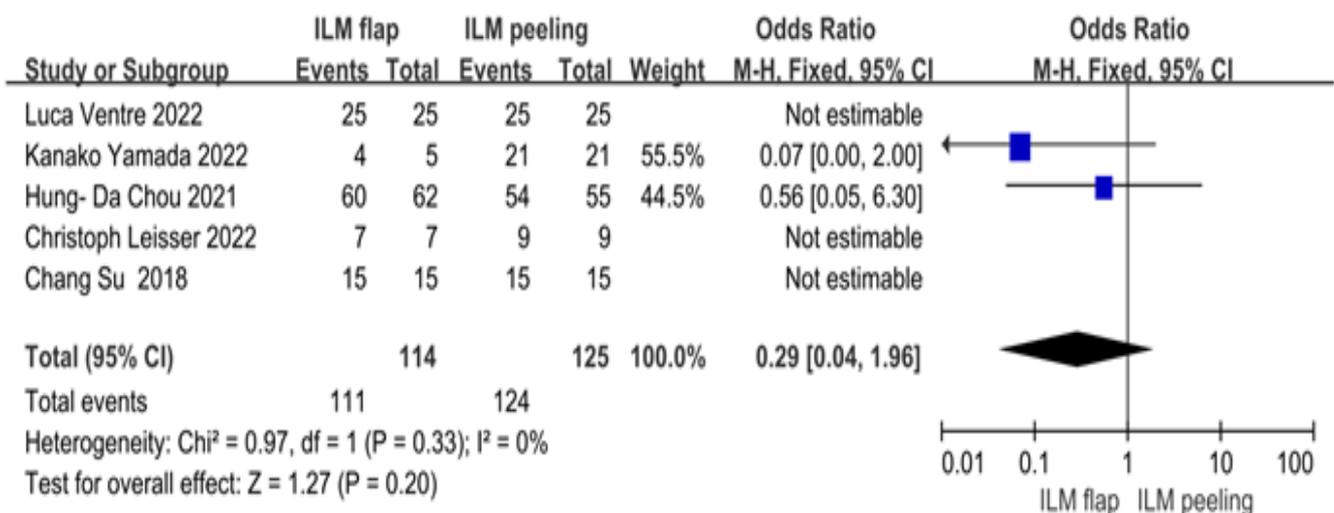
**Preoperative and postoperative visual acuity:** One of the six trials [17] didn't report preoperative and postoperative BCVA (converted to log MAR visual acuity for recording), which recorded Distance Corrected Visual Acuity (DCVA), thus the remaining five trials [16, 18-21] were analysed. Merging the data, no heterogeneity was revealed in preoperative BCVA ( $I^2=0\%$ , P=0.70) and postoperative BCVA ( $I^2=0\%$ , P=0.48) in each study, therefore, the fixed-effects model was used. These results suggested that the preoperative BCVA (WMD=-0.00, 95% CI: -0.24~0.24, P=0.70, Figure 3(A) and postoperative BCVA (WMD=-0.09, 95%CI: -0.33~0.15, P=0.48, Figure 3(B)) wasn't significantly different between two groups (Figure 3).

**Postoperative ELM recovery:** In four of six studies [16, 19-21] that observed the anatomical structure of the retina by Spectral-Domain Optical Coherence Tomography (SD-OCT), we compared the integrity of ELM after surgery in 3 months and 12 months between two groups. The heterogeneity was less than 50%, in which 3 months of  $I^2$  was 46% and 12 months of  $I^2$  was 13%, we chose the fixed-effects model. The ELM was completely intact in 100/109 (91.7%) eyes of the inverted ILM flap group and 134/144 (93.0%) of the ILM peeling group after 12 months. There was no significant

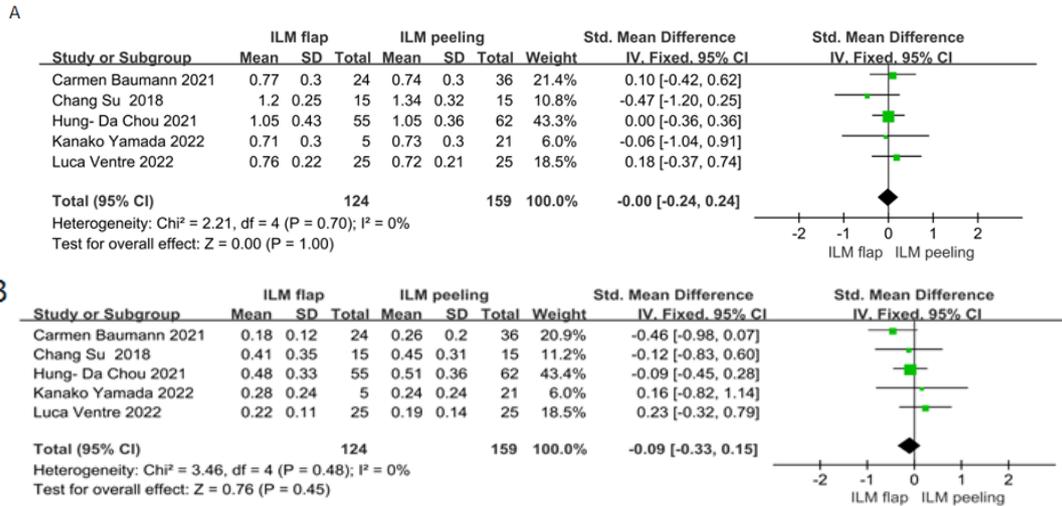
difference in the integrity of the ELM between patients who did or didn't receive an inverted ILM flap at either 3 months (OR=0.88, 95%CI: 0.39~1.97, P=0.16, Figure 4 (A)) or 12 months (OR=0.87, 95%CI: 0.30~2.54, P=0.33 Figure 4(B)) (Figure 4).

**Postoperative EZ recovery:** Four studies [16,19-21] recorded the structure of EZ, we collected 3 months and 12 months postoperatively as well. To merge data,  $I^2$  was 27% after 3 months and was 43% after 12 months, these were less than 50%, so the fixed-effects model was analyzed. The EZ was completely intact in 76/109 (69.7%) eyes of the inverted ILM flap group and 96/144 (66.7%) of the ILM peeling group after 12 months. The results showed that absence of significant differences was observed in postoperative EZ recovery between the control group, 3 months (OR=0.85, 95% CI: 0.47~1.53, P=0.25 Figure 5 (A)) and 12 months (OR=1.397, 95% CI: 0.79~2.46, P=0.15 Figure 5 (B), Figure 5).

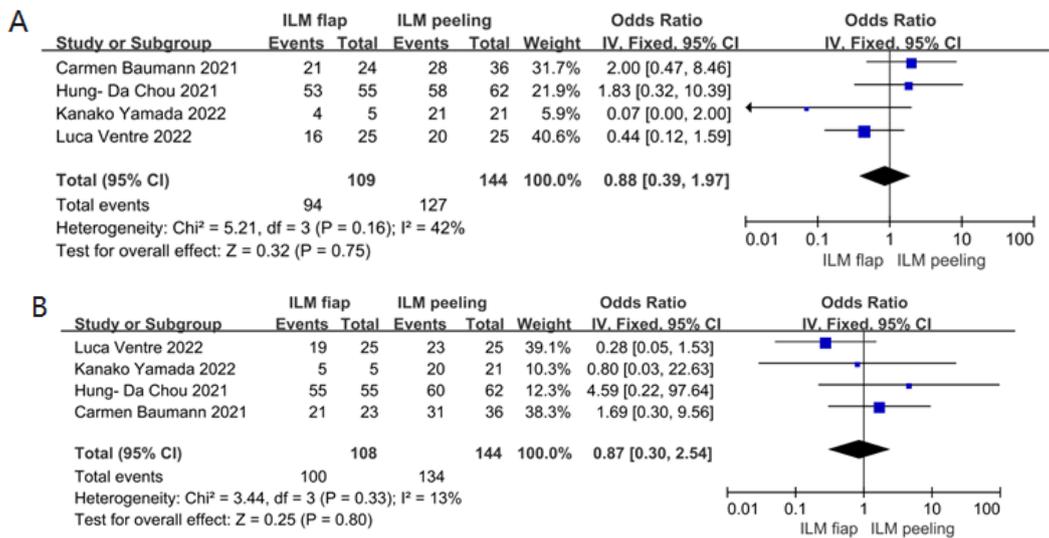
**Quality assessment:** We assessed the quality of the 3 RCTs [16-18] using Risk of Bias (RoB), which was a Cochrane collaboration tool. The clinical intervention of all included research in our meta-analysis was the surgical operation, so the operators and patients didn't use blind, but the results may be little affected by performance bias and selective bias. Except this study reported by Leisser Christoph, et al. [17] that had a low risk of bias in all assessing criteria and were assessed as high-quality trials, which had only 1 item with "unclear risk of bias" in Figure 6 and Figure 7. One research [17] was rated a low-quality trial because it missed some follow-up data. For 3 non-randomized controlled trials [19-21], we applied NOS to assess the studies' quality. All research were pointed to 6 stars or above that were high-quality research (Table 2).



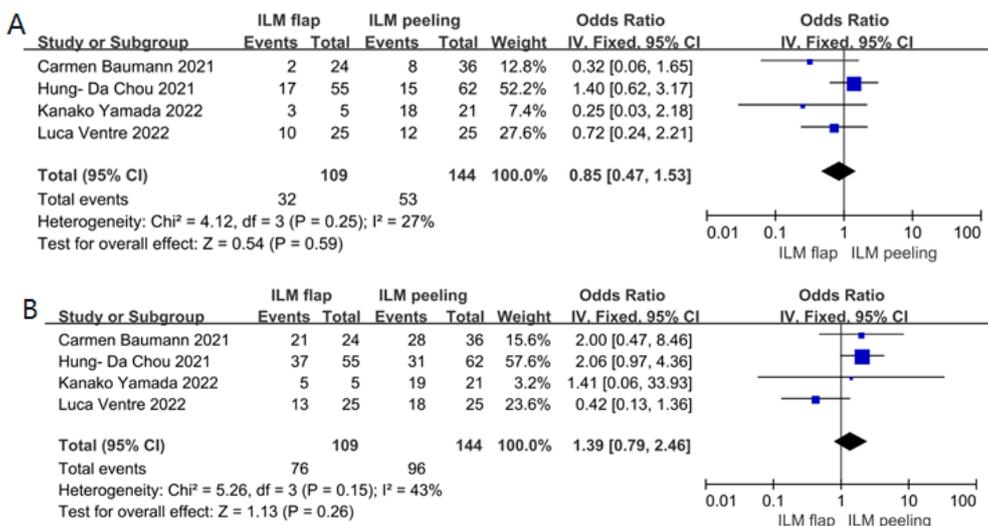
**Figure 2.** The effective rate of MH closure in the 2 groups Forest plot.



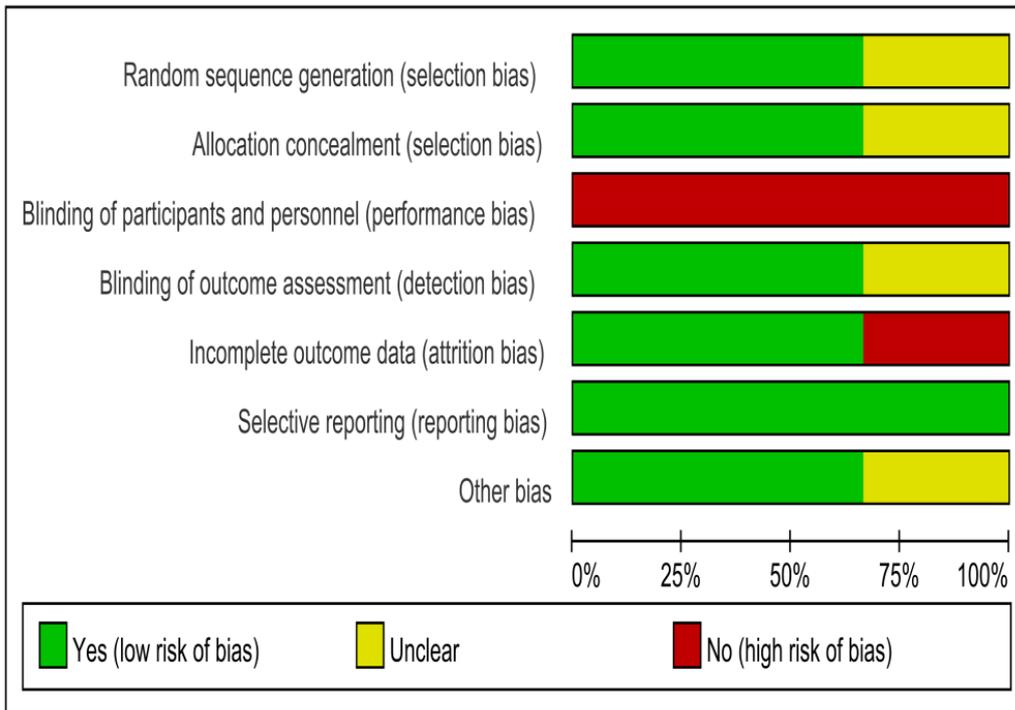
**Figure 3.** Forest plots of the BCVA before and after surgery. (A) Forest plot of the BCVA before surgery; (B) Forest plot of the BCVA after surgery.



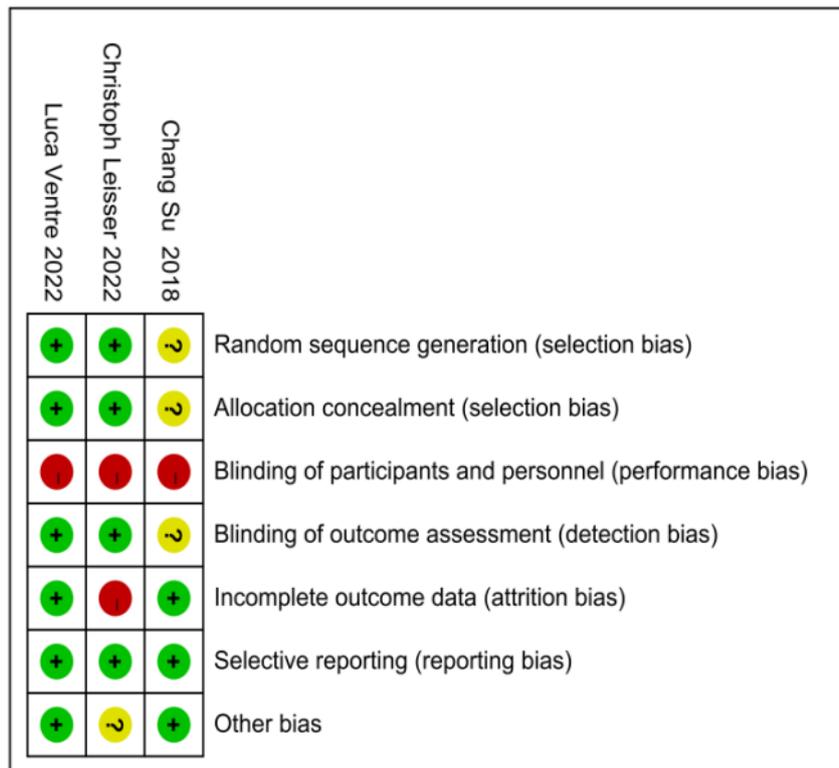
**Figure 4.** Forest plots of the integrity of ELM. (A) Forest plot of the integrity of ELM 3 months postoperatively; (B) Forest plot of the integrity of ELM 12 months postoperatively.



**Figure 5.** Forest plots of the integrity of EZ. (A) Forest plot of the integrity of EZ 3 months postoperatively; (B) Forest plot of the integrity of EZ 12 months postoperatively.



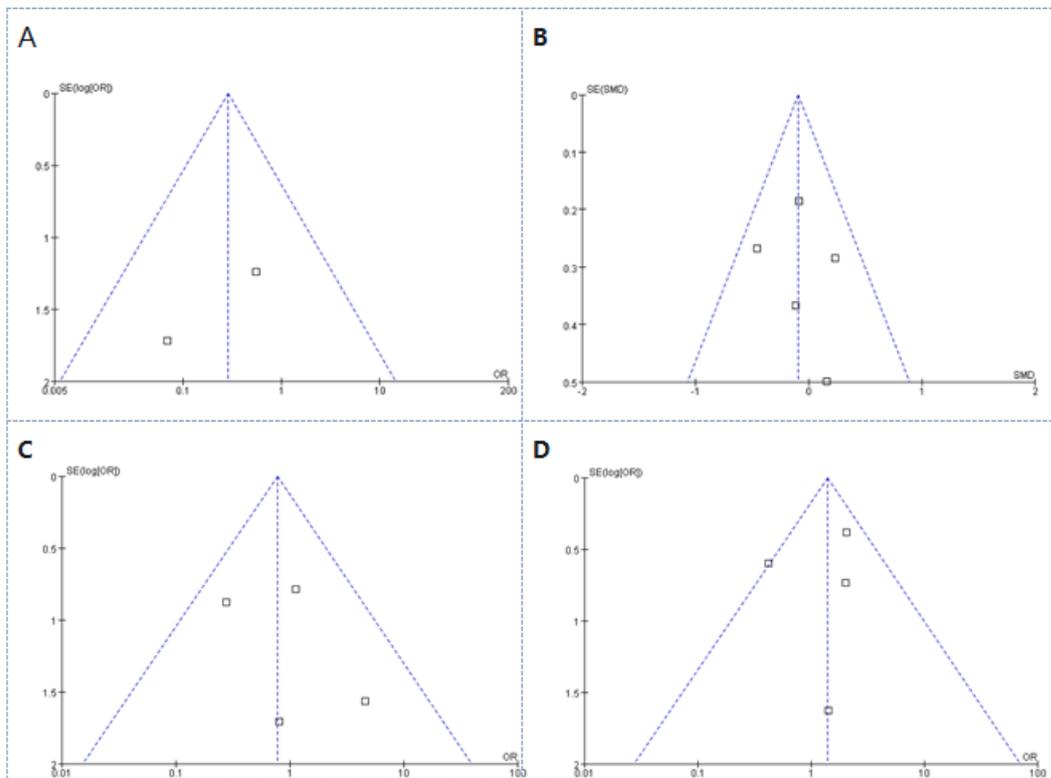
**Figure 6.** Risk of bias map. **Note:** (■): Yes (low risk of bias); (■): Unclear; (■): No (high risk of bias)



**Figure 7.** Risk of bias summary.

**Table 2.** Study methodology quality assessment on Newcastle-Ottawa scale (maximum score of 10).

Study (year)	Selection	Comparability	Exposure	Total
Hung-Da Chou (2021)	4	1	2	7
Carmen Baumann (2021)	4	2	2	8
Kanko Yamada (2022)	4	2	2	8



**Figure 8.** Funnel plot of publication bias. (A) Of the rate of MH closure; (B) Of the BCVA after surgery; (C) Of the integrity of ELM 12 months postoperatively; (D) Of the integrity of EZ 12 months postoperatively.

**Sensitivity analysis:** As it can be seen from the results of the above analysis, there was heterogeneity between all studies, and we conducted a sensitivity analysis by excluding studies with the largest and least weights to verify the stability of the results. The rate of MH closure, the visual acuity before and after surgery have no heterogeneity, we didn't conduct sensitivity analysis. When each study was excluded in the meta-analysis of postoperative 3 and 6 months of ELZ and EZ, there was no major change in the consequences. According to sensitivity analysis, all research of our meta-analysis was reliable.

**Publication bias analysis:** We assessed publication bias of the studies by funnel plots (Figure 8). No statistically significant evidence of publication bias was detected.

## Discussion

With the gradual deepening of knowledge about MH and the continuous innovation of various treatment options, there have been gradual improvement in hole closure after MH surgery. Inverted ILM flap technology is considered to be effective in clinical research, especially large MHs, complex MHs, and myopic MHs [9, 22-24]. Many meta-analysis and systematic reviews have recorded the advantages of the inverted ILM flap. However, there is a lack of such meta-analysis and systematic review: The efficacy of inverted ILM flap and traditional ILM peeling treatment in small and medium size

MHs. Thus, we made the first meta-analysis to compare the effective rate of hole closure and visual acuity improvement after surgery between the two groups to more reasonably guide the treatment of small and medium size MHs.

We conducted this systematic review and double-arm meta-analysis of the literature to summarize current evidence, compare the anatomical and visual outcomes of PPV with inverted ILM flap technique or ILM peeling. After pooling the results of the rate of MH closure in these studies, the rate wasn't different between the flap and peeling groups. Visual acuity was improved obviously in five studies [16, 18-21], but there was no evidence of a difference between the two groups as well. Furthermore, 4 studies [16, 19-21] recorded the healing of the ELM and EZ. The results exhibited an absence of significant variation in the integrity of the ELM or EZ at 3 months and 12 months between patients who received ILM flap or accepted conventional peeling. Our study suggests that inverted ILM flap and ILM peeling are equally effective in treating small and medium size MHs.

The inverted flap technique was first introduced by Michalewska, et al. [25] in 2010 to treat large MH, and they discovered the peeled-off ILM contains Müller cell fragments, which ILM peeling can induce gliosis to enhance closure. Moreover, the inverted ILM flap provided a scaffold for tissue proliferation, in which cells

always need a basement membrane to proliferate. The same hypothesis was proved by Kurt Spiteri, et al. [26]. On the one hand, type IV collagen, protein fiber connections, and laminin in the ILM can promote Müller cells proliferation and migration, inducing the retina move towards the center. On the other hand, the ILM flap separated the outer retina from the vitreous, reducing the hydration affection, maintaining the central fovea to reshape, and bringing a good vision outcome [27]. However, there are always controversial about inverted ILM flap. Iwasaki, et al. [28] thought that the ILM flap technique restricted the refractory MH. They observed the poorer anatomical and visual results associated with inverted ILM flap compared with ILM peeling by studying 24 patients of MH. The reason may be different surgical options, they filled some ILM in the hole to cause anatomical damage and scar tissue, thereby leading to a different ending. Our meta-analysis excluded this influence, all surgeons used a single flap to cover the hole in six studies.

We observed ELM and EZ recovery after surgery at 3 months and 12 months in two groups, 3 months replacing short-term effect and 12 months replacing relatively long-term effect. The integrity of the ELM and EZ appeared to have critical roles in the restoration of the photoreceptor microstructures [29]. EZ is the only marker band to determine whether the photoreceptor cells are alive [30]. Some studies have also reported that postoperative ELM and EZ integrity represent a key prognostic factor for photoreceptor layer recovery, which had a positive visual outcome after MH surgery [29, 31-33]. Although the two groups have no obvious difference in our meta-analysis, a continuous ELM could be observed postoperatively of most patients in a short time. A fully regenerated ELM was identified to be essential for EZ regeneration [34, 35]. Our study also validated this finding. Chou, et al. [19] found an earlier restoration of ELM in the inverted flap group compared with conventional ILM peeling: The rate of ELM restoration was higher in the inverted flap group at 1 and 3 months, while this was comparable between the two groups at 12 months. Other research evidenced the same view [36, 37]. Masayuki Horiguchi, et al. [38] compared operated eyes with inverted ILM flap and with normal fellow eyes by multifocal electroretinograms that found the upper retina without the ILM flap and the lower retina covering the ILM flap have no significant difference. These related studies indicated that the inverted ILM flap technology didn't cause worse functional and morphological outcomes.

### Limitations of the Study

Our study has several limitations. Only two RCTs were rated as high-quality, and these studies had small sam-

ple sizes and insufficient follow-up time, which may have resulted in certain selection and information biases. Third, due to baseline information inadequacy, such as gender, symptom continuance time, and so on, the effects of various factors weren't analysed. Further prospective studies with large sample sizes are necessary to validate our study.

### Conclusion

In conclusion, there was evidence favouring inverted ILM flap about BCVA at 12 months, final macular hole closure, and retina anatomical structure with no deterioration, it was considered to be equal treatment effective with ILM peeling. Accordingly, this therapeutic approach may be advisable for the treatment of patients with <400 µm MHs.

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### Contributions

P.P.L. took part in designing the research, collected the data, analyzed the results and wrote the manuscript. L.L. designed the research, revised the manuscript and supervised all the work. J.H.W. screened titles, abstracts, and full-text articles, abstracted and cleaned data, conducted quality assessment, and solved the disagreements between P.P.L. and L.L., All authors read and provided suggestions during manuscript preparation.

### Competing Interests

The authors declare no competing interests.

### Additional Information

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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