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SYSTEMATIC REVIEW

Management of Macular Hole: Pharmacological, Procedural, and Surgical Treatment-A Systematic Review

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Abstract

Background: Full-thickness macular hole (FTMH) impairs central vision. Although pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling and gas tamponade is the standard treatment, the comparative effectiveness of surgical modifications, adjunctive therapies, and selected nonsurgical approaches remains uncertain.

Methods: This PRISMA 2020 systematic review was prospectively registered in PROSPERO (CRD420261391937). PubMed/MEDLINE was searched for English-language randomized controlled trials published between January 2016 and April 2026. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane RoB 2 tool. Owing to methodological heterogeneity, findings were synthesized narratively.

Results: Twenty-three randomized controlled trials were included. PPV with ILM manipulation achieved high anatomical closure rates, although no intervention was consistently superior across all clinical scenarios. Inverted ILM flap, ILM repositioning, and wider or 360° ILM peeling improved closure in selected large or complex holes, whereas tissue-sparing techniques better preserved retinal architecture and retinal sensitivity. Sulfur hexafluoride (SF6) achieved higher single-surgery closure than air for small-to-medium holes, while no clear superiority was demonstrated among expansile gases. Improvements in anatomical closure did not consistently translate into superior visual outcomes. Most studies had some risk-of-bias concerns.

Conclusions: Current randomized evidence supports PPV with ILM manipulation as the cornerstone of FTMH management. Surgical techniques should be individualized according to hole characteristics, balancing anatomical closure with retinal preservation. Higher quality randomized trials with standardized anatomical, functional, and safety outcome reporting are needed.

Introduction

Full-thickness macular hole (FTMH) is a vitreoretinal disorder characterized by a full-thickness defect of the neurosensory retina at the fovea, resulting in disruption of central macular architecture. Because the fovea is responsible for high-resolution central vision, FTMH can lead to reduced visual acuity, central scotoma, metamorphopsia, and impairment of reading and daily visual function. Although macular holes were historically first described in association with ocular trauma, most FTMHs encountered in clinical practice are idiopathic and related to age-associated vitreomacular interface changes [1,2].

FTMH is relatively uncommon but clinically important. A population-based study from Olmsted County, Minnesota reported an annual incidence of idiopathic macular holes of 7.8 persons per 100,000 population and 8.69 affected eyes per 100,000 population per year, with female predominance [3]. More recent nationwide population-based data from Korea reported an idiopathic macular hole incidence of approximately 10.63 per 100,000 person-years, with higher risk in older age groups and among women [4]. These epidemiological findings highlight that, although FTMH is not highly prevalent, its clinical impact is meaningful because it affects central vision in an older population.

Optical coherence tomography (OCT) has become central to the diagnosis, classification, and management of macular holes. The International



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Vitreomacular Traction Study Group proposed an OCT based classification system for vitreomacular adhesion, vitreomacular traction, and macular holes, including classification according to hole size, presence or absence of vitreomacular traction, and whether the hole is primary or secondary [5]. This classification is clinically relevant because anatomical and visual outcomes are influenced by baseline hole size, chronicity, vitreomacular traction status, and associated ocular pathology.

Pars plana vitrectomy with posterior hyaloid separation, internal limiting membrane (ILM) peeling, and intraocular gas tamponade remains the mainstay of surgical management for FTMH. ILM peeling has been shown to improve anatomical and visual success in macular hole surgery and reduce reopening in larger holes [6,7]. Conventional surgery achieves high anatomical closure rates in many idiopathic cases; however, outcomes may be less predictable in large, chronic, recurrent, myopic, or otherwise complex macular holes [8].

As a result, several surgical modifications and adjunctive strategies have been introduced to improve anatomical closure, enhance foveal remodeling, and reduce the risk of persistent or recurrent holes. These include variations in ILM peeling extent, inverted ILM flap techniques, fovea sparing approaches, modified flap fixation methods, different gas tamponade agents, and combined phacovitrectomy strategies [8,9]. The inverted ILM flap technique, in particular, was introduced for large macular holes and has been proposed to improve both anatomical and functional outcomes in selected complex cases [9].

Biological adjuncts have also been proposed, particularly for large, recurrent, or refractory macular holes. These include autologous platelet concentrate, platelet rich plasma, autologous serum, lens capsule flap transplantation, and autologous retinal transplantation. These approaches aim to provide a scaffold or biologically active substrate that may promote tissue bridging, glial proliferation, and restoration of foveal anatomy [10-13].

Less invasive approaches have also been explored in selected patients, particularly for early or small macular holes associated with vitreomacular traction. Pharmacological vitreolysis has been proposed as a strategy to release vitreomacular traction or promote closure without immediate vitrectomy [14]. Pneumatic vitreolysis has also been explored in selected patients, their success is likely influenced by hole size, chronicity, lens status, and the presence of persistent vitreomacular adhesion. Therefore, these approaches require careful evaluation alongside established surgical interventions.

Despite the expanding range of available interventions, the comparative effectiveness and safety

of different FTMH management strategies remain uncertain. Existing studies vary in patient selection, macular hole size, surgical technique, tamponade choice, follow-up duration, and outcome reporting [7,8]. This heterogeneity makes it difficult to draw firm conclusions from individual studies alone. Therefore, a systematic review of randomized evidence is needed to summarize anatomical, visual, OCT based, functional, and safety outcomes across available surgical, pharmacological, and adjunctive interventions for FTMH.

Objective

This systematic review aims to evaluate randomized controlled evidence on surgical, adjunctive, and selected nonsurgical interventions for full-thickness macular holes. The primary outcome is anatomical macular hole closure, while secondary outcomes include visual acuity improvement, OCT based structural or functional recovery, complications, recurrence, and the need for additional intervention.

Methods

Study design and reporting guideline

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [15] and was prospectively registered in PROSPERO (CRD420261391937). Two protocol deviations were made during the review and are reported transparently: eligibility was refined to randomized controlled trials (RCTs) only, to focus on the highest level of comparative evidence for full-thickness macular hole management; and although the registered protocol listed both PubMed/MEDLINE and CENTRAL, the final search was restricted to PubMed/MEDLINE. These deviations were considered when interpreting the completeness of the evidence base. Given the heterogeneity of interventions, comparators, outcome definitions, and follow-up durations, findings were synthesized narratively rather than by meta-analysis.

Eligibility criteria

Studies were considered eligible if they were randomized controlled trials evaluating an intervention for the management of full-thickness macular holes. Eligible populations included patients with idiopathic full-thickness macular holes and, where applicable, secondary macular holes when the study assessed a therapeutic intervention directed at macular hole closure or visual recovery. Eligible interventions included surgical, pharmacologic, and adjunctive approaches, such as pars plana vitrectomy, internal limiting membrane peeling, inverted or modified internal limiting membrane flap techniques, different peeling extents, tamponade agents, pharmacologic vitreolysis, and other adjunctive techniques used for macular hole repair.

Comparative randomized studies were included when they reported at least one clinically relevant anatomical, functional, or safety outcome. The main outcomes of interest were anatomical macular hole closure, best-corrected visual acuity, macular hole size, optical coherence tomography findings, external limiting membrane or ellipsoid zone recovery, postoperative complications, and need for reoperation. Studies were excluded if they were non-randomized, non-comparative, observational studies, case reports, case series, reviews, animal studies, pediatric studies, or studies that did not specifically evaluate treatment outcomes for full-thickness macular holes. Studies of lamellar macular holes, non-macular-hole retinal disease, postoperative macular changes without primary treatment outcomes, and persistent or recurrent macular holes were also excluded.

Information source and search strategy

A systematic literature search was conducted in PubMed/MEDLINE. The final search was performed on May 2, 2026. The search strategy combined terms related to macular hole with terms for relevant interventions and outcomes, including vitrectomy, internal limiting membrane peeling, inverted flap techniques, tamponade, pharmacologic vitreolysis, anatomical closure, visual acuity, and optical coherence tomography outcomes. The search was limited to human studies published in English between 2016 and 2026. Randomized controlled trials were prioritized according to the final eligibility criteria.

The PubMed search string was as follows

("Macular Hole"[Mesh] OR "macular hole"[tiab] OR "macular holes"[tiab] OR "full-thickness macular hole"[tiab], OR "idiopathic macular, hole"[tiab]) AND (vitrectomy[tiab] OR "pars plana vitrectomy"[tiab] OR PPV[tiab] OR ocriplasmin[tiab] OR microplasmin[tiab] OR "pneumatic vitreolysis"[tiab] OR "intravitreal gas"[tiab] OR "gas tamponade"[tiab] OR "silicone oil"[tiab] OR "internal limiting membrane"[tiab] OR ILM[tiab] OR "ILM peeling"[tiab] OR "ILM flap"[tiab] OR "inverted flap"[tiab] OR "autologous serum"[tiab] OR "platelet-rich plasma"[tiab] OR PRP[tiab]) AND (closure[tiab] OR "anatomical closure"[tiab] OR "visual acuity"[tiab] OR BCVA[tiab] OR logMAR[tiab] OR complication*[tiab] OR recurrence[tiab] OR outcome*[tiab]).

Study selection

All identified records were imported into Rayyan and duplicates removed [16]. Two reviewers independently screened titles and abstracts, then assessed full texts against the predefined inclusion and exclusion criteria, with final inclusion limited to randomized controlled trials of comparative interventions for full-thickness macular hole management. Disagreements were resolved by discussion, with unresolved cases planned

for consultation with a third reviewer. Reasons for exclusion at the full-text stage were recorded, and the selection process is presented in a PRISMA 2020 flow diagram (Figure 1).

Data extraction

Data were extracted using a standardized extraction form. Extracted variables included study identification, year of publication, country, design, setting, sample size and the number of patients or eyes analyzed, participant and macular-hole characteristics (type and baseline size), intervention and comparator, surgical technique, tamponade agent, follow-up duration, and reported outcomes.

The main outcomes were anatomical closure rate and type, best-corrected visual acuity at baseline and follow-up and its change, OCT outcomes, ellipsoid zone or external limiting membrane recovery, macular hole size change, complications, recurrence, and reoperation. Numerical data were extracted as raw numbers, percentages, means with standard deviations, medians with ranges or interquartile ranges, and p-values; when reported separately by arm, data were extracted for each arm independently. Where multiple follow-up time points were reported, the final follow-up was prioritized while clinically relevant earlier outcomes were also recorded, and all extracted data were cross-checked against the full text articles (Table 1).

Risk of bias assessment

Two reviewers independently assessed risk of bias using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) [17]. The following domains were considered: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcomes, and bias in selection of the reported result. Each study was judged as having low risk of bias, some concerns, or high risk of bias. Disagreements were resolved through discussion (Figure 2).

Showing RoB 2 judgments for each included randomized controlled trial across the domains D1 randomization process, D2 deviations from intended interventions, D3 missing outcome data, D4 measurement of the outcome, D5 selection of the reported result, and overall risk of bias. Green circles with a plus sign indicate low risk of bias, yellow circles with an exclamation mark indicate some concerns, and red circles with a minus sign indicate high risk of bias. Judgments were extracted directly from the RoB2 Tracker sheet without modification.

Showing the proportion and number of included randomized controlled trials rated as low risk, some concerns, or high risk for each RoB 2 domain and for the overall risk-of-bias judgment. Percentages are

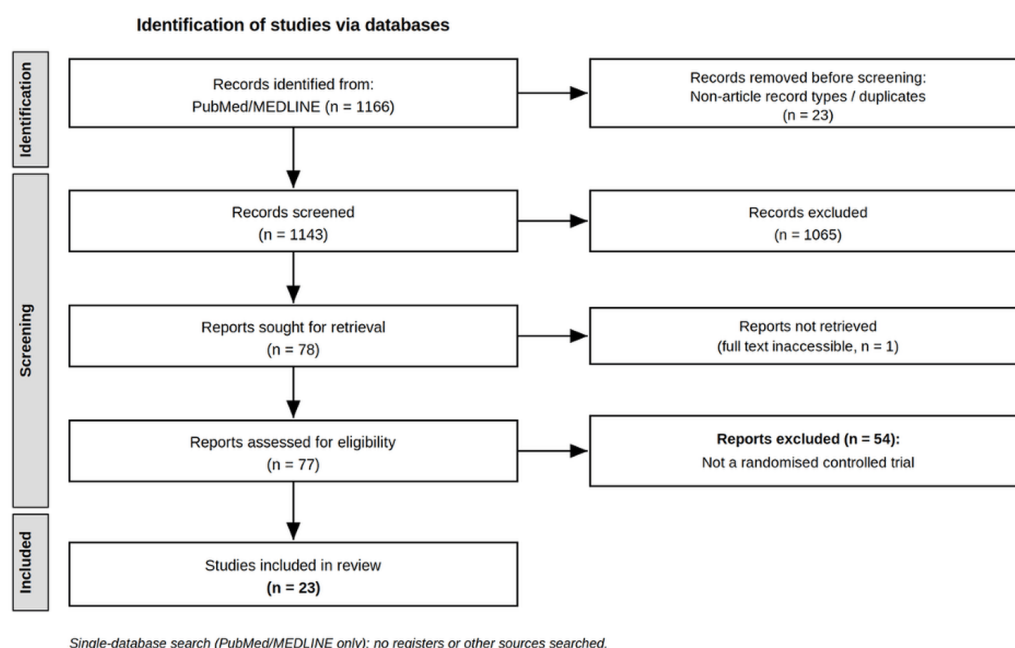


Figure 1: Prisma 2020 flow diagram of study identification, screening, and inclusion. A single-database search of PubMed/MEDLINE identified 1166 records; 23 non-article or duplicate records were removed before screening. Of 1143 records screened, 1065 were excluded at title and abstract. Of 78 reports sought for retrieval, 1 was not retrieved (full text inaccessible) and 54 were excluded at full text because they were not randomised controlled trials, leaving 23 studies included in the review.

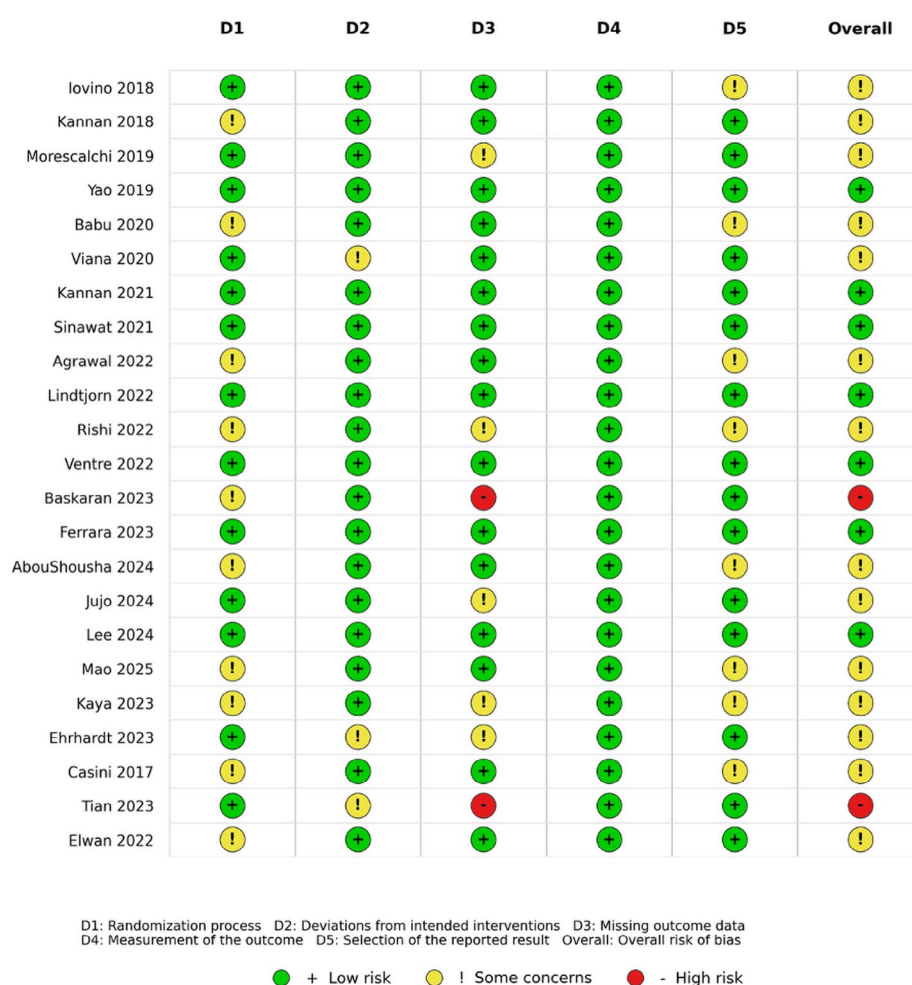


Figure 2: Risk-of-bias assessment for included randomized controlled trials (RoB 2).

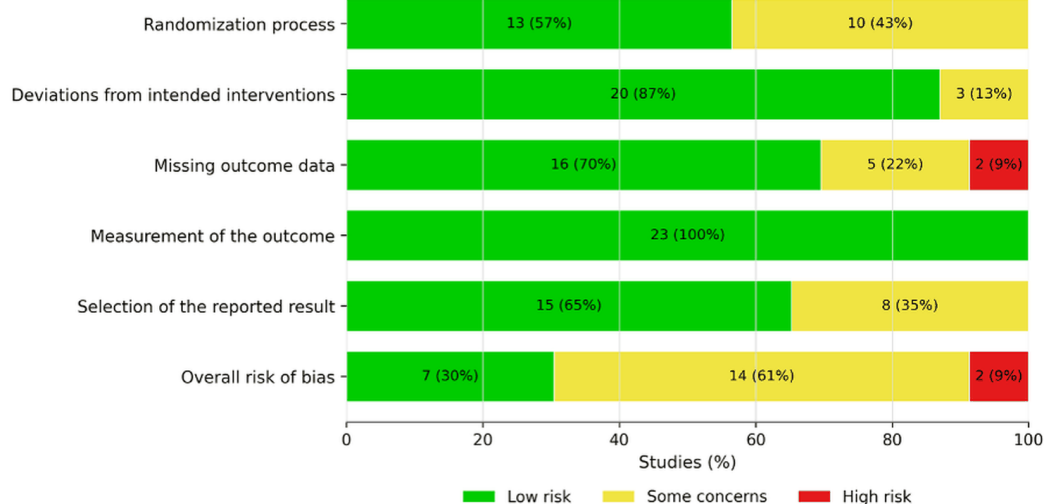


Figure 3: Summary of RoB 2 judgments across included randomized controlled trials.

calculated using the included randomized controlled trials listed in the RoB2 Tracker sheet (Figure 3).

Data synthesis

A narrative synthesis was performed because meta-analysis was not considered appropriate due to substantial heterogeneity in interventions, comparators, patient populations, surgical techniques, outcome definitions, and follow-up durations. Studies were grouped according to intervention category: ILM peeling extent or preservation, inverted or modified ILM flap techniques, tamponade comparisons, combined pars plana vitrectomy and phacoemulsification versus deferred cataract surgery, dye-assisted ILM peeling, instrument- or intraoperative OCT-guided techniques, and pharmacological adjunctive therapy.

Within each category, anatomical closure, visual acuity outcomes, OCT based or functional outcomes, complications, recurrence, and need for additional intervention were summarized. Direction of effect was described qualitatively, and conclusions were interpreted in light of risk of bias and certainty of evidence.

Results

Study selection and evidence profile

Twenty-three RCTs evaluating management strategies for FTMH were included. The extracted randomized sample comprised 1,624 reported study units and the analyzed sample 1,564 reported study units; these totals should be interpreted cautiously because trials did not consistently specify whether the denominator represented patients or eyes, and denominators varied across anatomical, visual, OCT, safety, and reoperation outcomes owing to attrition, post-randomization exclusions, rescue procedures, and

per-protocol analyses. Trials were grouped by the main strategy tested: 11 evaluated ILM flap, repositioning, or flap-variant techniques versus conventional peeling or another ILM-based approach [18-28]; 4 evaluated ILM peeling extent or tissue-sparing modifications, including wider, hemi-temporal, and fovea-sparing peeling [29-32]; and 3 compared gas tamponade after PPV [33-35]. Single-study categories evaluated topical dorzolamide [36], platelet-rich plasma (PRP) [37], heavy brilliant blue G (hBBG) staining [38], timing of cataract surgery with PPV [39], and ILM forceps type [40]. Follow-up generally ranged from 6 weeks to 12 months. Because hole size, staging, surgical technique, tamponade, and outcome definitions were heterogeneous, results were summarized narratively. Staging was not reported uniformly-some trials used Gass stage and others OCT size thresholds (≤ 400 , >400 , >500 , >600 , or >800 μm)-so the evidence was interpreted across three groupings: Early/small holes, small to-medium established FTMHs, and larger or advanced/complex FTMHs.

Anatomical closure and reoperation

Anatomical closure was generally high after PPV-based treatment with ILM manipulation, but no intervention was consistently superior across presentations. In small to-medium holes, conventional ILM peeling achieved high closure: Ventre, et al. reported 100% closure with both conventional peeling and inverted flap [28], and Kannan, et al. reported 100% with both hBBG-assisted and unstained peeling [38]. Lindtjörn, et al. provided the clearest tamponade signal, with higher single surgery closure using SF6 than air in the intention-to-treat analysis (100% [75/75] vs. 86.7% [65/75]; $P = 0.001$), although final closure reached 100% in both arms after second surgery [34]. Jujo, et al. found higher primary closure with 360° than hemi-temporal peeling (100% [23/23] vs. 73.9% [17/23]; $P = 0.009$), with all eyes closing after rescue treatment [29].

Table 1: Characteristics of included studies.

Study (year)	Country	Design	Intervention vs. comparator	MH type and baseline size	Sample size (per arm)	Anatomical closure	Follow-up
Abou Shousha 2024	Egypt	Single-centre RCT	“Flip and Fix” flap vs PFCL-assisted temporal flap	Idiopathic FTMH; mean min. diameter 561 vs. 597 µm	11 vs 11 eyes (22 eyes / 22 patients)	100% (11/11) vs. 90.9% (10/11)	6 months
Agrawal 2022	India	Single-centre RCT	Multilayered inverted ILM flap (under PFCL) vs. standard ILM peeling	Large idiopathic FTMH (base diameter >600 µm); mean min. diameter 766 (flap) / 750 (peel) µm	150 eyes (75 / 75) patients	Flap 100% (75/75) vs. peel 93.3% (70/75); Type 1 closure 93.3% Vs. 78.7% (P = 0.0001)	12 months
Babu 2020	India	Single-centre pilot RCT	Platelet-rich plasma (PRP) vs. inverted ILM flap	Idiopathic large FTMH 600-1500 µm, pseudophakic; mean min. diameter 785 (PRP) / 803 (flap) µm	60 patients (30 / 30); 1 eye each	PRP 93.3% (28/30) vs. flap 90% (27/30) (P = 0.158); Type 1 closure 83.3% vs 76.7%	3 months
Baskaran 2023	India	Single-centre, double-blind RCT	PFO-assisted inverted ILM flap vs. conventional ILM peeling	Large idiopathic FTMH (aperture >500 µm); mean min. diameter 721 (flap) / 677 (peel) µm	99 eyes (54 flap / 45 peel); 97 analysed	Flap 100% (27/27) vs. peel 90% (18/20) at 12 mo (P = 0.176); flap significantly higher at 1 mo (89.8% vs. 62.5%) and 6 mo (100% vs 80.8%)	12 months
Casini 2017	Italy	Single-centre, single-masked RCT	Classic inverted flap vs inverted flap without extra manipulation; large MH >400 µm	Idiopathic FTMH, stage IV, large (>400 µm); mean min. diameter 561 vs 603 µm	41 vs 40 eyes (81 eyes / 78 patients)	97.6% (40/41) vs. 97.5% (39/40)	12 months
Ehrhardt 2023	France	Single-centre, open-label RCT	Temporal inverted ILM flap vs. conventional (complete) ILM peeling	Idiopathic MH >250 µm; median min. diameter 405 (flap) / 375 (peel) µm	65 patients; 60 analysed (30 / 30)	93.3% (28/30) in both groups (P = 1.00); 100% in both after second surgery	3 months (subset to 15-18 months)
Elwan 2022	Egypt	Single-centre RCT	Small (1–2 DD) vs large (2–4 DD) inverted ILM flap	Large idiopathic MH >400 µm; mean min. diameter ~590 µm	25 eyes (13 small / 12 large)	Small flap 84.6% (11/13) vs. large flap 91.6% (11/12) at 6 mo (P = 1.00)	6 months
Ferrara 2023	UK	Masked proof-of-concept RCT	Etched-tip vs. smooth-tip ILM forceps	Idiopathic FTMH, any size; mean min. diameter 450 vs. 473 µm	65 eyes operated; 33 vs. 32 per arm	95.4% overall (62/65); not reported per arm	6 months
Iovino 2018	Italy	Two-centre RCT	Subretinal fluid aspiration vs. inverted ILM flap	Stage IV FTMH >400 µm, pseudophakic; mean min. diameter ~665 µm	40 eyes (20 / 20)	100% (20/20) in both groups after first surgery	6 months
Jujo 2024	Japan	Multicentre (3 sites) RCT	Hemi-temporal vs. 360° ILM peeling	Idiopathic MH <400 µm, <6 mo duration; mean min. diameter 256 (hemi) / 239 (360°) µm	50 eyes; 46 analysed (23 / 23)	Hemi-temporal 73.9% (17/23) vs. 360° 100% (23/23) (P = 0.009); 100% in both after second surgery	6 months
Kannan 2018	India	Single-centre RCT	ILM peel vs inverted ILM flap; large MH 600–1500 µm	Idiopathic FTMH, large (600–1500 µm); mean min. diameter 760 vs 803 µm	30 vs. 30 eyes	76.7% (23/30) vs. 90% (27/30), P = 0.166; Type 1 70% vs 90%	6 months
Kannan 2021	India	Single-centre, single-blind RCT	ILM peel + hBBG staining vs. no staining	Idiopathic FTMH, stage ≥ 2 (<800 µm); mean size 563 vs. 548 µm	24 vs. 20 eyes (44 eyes / 42 patients)	100% vs. 100%	6 months

Kaya 2023	Turkey	Single-centre RCT	C3F8 (14%) vs. SF6 (20%) tamponade	Idiopathic FTMH, stage 34 (>400 µm); mean min. diameter 498 vs. 479 µm	20 vs 18 eyes (38 eyes / 38 patients; 42 randomized)	Closed-MH cohort by design	3 months
Lee 2024	Australia	Single-centre, double-blind, placebo-controlled RCT	Topical dorzolamide 2% vs. placebo (saline)	Idiopathic small FTMH <400 µm; mean diameter ~205 µm	32 patients (16 / 16)	18.8% (3/16) in both groups at 8 wk (P = 1.00); all persistent holes closed after rescue vitrectomy	8 weeks (then surgery if persistent)
Lindtjørn 2022	Norway	Multicentre (5 sites) noninferiority RCT	Air vs. SF6 gas tamponade (after PPV + ILM peel)	Primary MH ≤ 400 µm (small ≤ 250 / medium >250-400); median size 294 / 300 µm	150 patients (75 / 75)	Air 86.7% (65/75) vs. SF6 100% (75/75), ITT (P = 0.001); 100% in both after second surgery	Closure 2–8 weeks; last follow-up ~23–33 days
Mao 2025	China	Single-centre pilot RCT	iOCT partial peel + inferior flap vs. standard peel; Gass stage 4	Idiopathic MH, Gass stage 4; mean diameter 458 vs. 471 µm	18 vs. 16 eyes (34 eyes / 34 patients)	94.4% (17/18) vs. 87.5% (14/16), P = 0.26 ^c	6 months
Morescalchi 2019	Italy	Single-centre RCT	Complete vs. fovea-sparing ILM peel; MH >250 µm	Primary FTMH, medium/large (>250 µm); mean diameter 640 vs 610 µm	22 vs. 22 eyes (46 eyes / 45 patients)	96% (22/23) vs. 100%	12 months
Rishi 2022	India	Single-centre, 3-arm RCT	C3F8 vs. C2F6 vs. SF6 tamponade; stage III/IV	Idiopathic MH, stage III-IV; stratified <800 / >800 µm apical; overall mean min. diameter 549 µm	72 vs. 50 vs. 37 eyes (159 eyes)	Type 1: C3F8 74% / C2F6 80% / SF6 70%, P = 0.556 ^d	2 months
Sinawat 2021	Thailand	Single-centre RCT	1-DD vs. 2-DD (extended) conventional ILM peeling	Large idiopathic FTMH (MLD >400 µm); mean MLD ~633 µm	104 eyes; 100 analysed (49 1-DD / 51 2-DD)	1-DD 51.0% (25/49) vs. 2-DD 76.5% (39/51) (P = 0.008)	6 months
Tian 2023	China	Single-centre, double-blind pilot RCT	Peeled ILM reposition vs. ILM peeling	Idiopathic MH ≤ 600 µm; mean diameter 371 / 366 µm	30 patients; 27 analysed (13 reposition / 14 peel) ^e	Reposition 86.7% (13/15) vs. peel 93.3% (14/15) (P = 0.60); 100% in both after second surgery ^e	6 months
Ventre 2022	Italy	Single-centre RCT	Conventional ILM peeling vs inverted flap	Small-to-medium idiopathic FTMH ≤ 400 µm; mean diameter 254 (peel) / 269 (flap) µm	50 eyes (25 / 25)	100% (25/25) in both groups	12 months
Viana 2020	Brazil	Single-centre, examiner-masked RCT	Combined PPV/phaco vs. PPV/deferred phaco	Idiopathic FTMH, stage ≥ II; mean min. diameter 469 vs. 473 µm	33 vs. 32 patients (34 vs. 34 randomized); one study eye each ^f	73% vs. 75%, P = 0.834	12 months
Yao 2019	China	Single-centre, noninferiority RCT	2DD vs. 4DD extent of ILM peel; idiopathic FTMH	Idiopathic FTMH (≤ 3 yr duration); mean min. diameter 476 vs. 493 µm	63 vs. 58 eyes (121 eyes / 121 patients)	82.5% (52/63) vs. 91.4% (53/58), P = 0.185 ^g	12 months (54 weeks)

Abbreviations: BBG: Brilliant Blue G; BCVA: Best-Corrected Visual Acuity; DD: Disc Diameter; FTMH: Full-Thickness Macular Hole; HBBG: Heavy Brilliant Blue G; ILM: Internal Limiting Membrane; IOCT: Intraoperative Optical Coherence Tomography; ITT: Intention-To-Treat; MH: Macular Hole; MHCI: Macular Hole Closure Index; min: Minimum; MLD: Minimum Linear Diameter; OCTA: OCT Angiography; PFCL/PFO: Perfluorocarbon Liquid / Perfluoro-n-Octane; PPV: Pars Plana Vitrectomy; SF6: Sulfur Hexafluoride

In large, stage three and four or anatomically challenging holes, flap and repositioning techniques produced high closure but variable comparative advantage. Baskaran, et al. reported higher early closure with PFO-assisted inverted flap at 1 and 6 months, but the 12 month difference was no longer significant (100% vs. 90.0%; $P = 0.176$) [20]. Agrawal, et al. reported complete closure with multilayered inverted flap versus 93.3% with standard peeling [19]. Kannan, et al. found numerically higher closure with inverted flap than peeling (90.0% vs. 76.7%; not significant) [25]. Other flap or repositioning trials reported similar closure between arms, including temporal inverted flap versus conventional peeling [22], aspiration-assisted technique versus inverted flap [24], small versus large inverted flap [23], iOCT-guided partial flap versus standard peeling [26], and ILM repositioning versus peeling [27].

Peeling-extent trials suggested that broader or complete peeling may improve closure in selected configurations. Sinawat, et al. reported higher closure with 2- than 1-disc-diameter peeling in large holes (76.5% vs. 51.0%; $P = 0.008$) [31]. Yao, et al. found no significant overall difference between 2- and 4-disc-diameter peeling but superiority of 4-disc-diameter peeling in the MHCI ≤ 0.5 subgroup (76.9% vs. 18.2%; $P = 0.012$) [32]. Morescalchi, et al. reported high closure with both complete and foveaparing peeling [30]. PRP and inverted ILM flap produced similar closure in one pilot trial of large holes [37]. Among expansile gases, Rishi et al. found no significant closure difference among SF6, C2F6, and C3F8 [35], while Kaya, et al. could not support a reliable primary-closure comparison because unclosed holes were excluded from the analyzed cohort [33].

Reoperation was mainly related to primary nonclosure. Ten air-treated eyes in Lindtjörn, et al. required second surgery or SF6, whereas no SF6-treated eyes required additional surgery [34], and six nonclosures after hemi-temporal peeling in Jujo, et al. closed after secondary surgery or additional gas [29]. In most flap and adjunctive trials, reoperation numbers were small and inconsistently reported.

BCVA, OCT, and functional outcomes

BCVA improved in most surgical trials, but anatomical advantages did not consistently translate into significant between group differences. Several flap and repositioning trials showed no significant final BCVA difference despite high closure in both arms [20-22,25,26,28]. Favorable visual signals were reported in selected trials, including better postoperative BCVA with the aspiration-assisted technique than inverted flap [24], with larger than smaller inverted flap [23], with multilayered inverted flap than standard peeling at 12 months [19], and after ILM repositioning than peeling at 6 months [27]. In peeling-extent trials, wider peeling improved closure in some studies without consistently

improving overall BCVA, although Yao, et al. reported better final BCVA with 4-disc-diameter peeling in the MHCI ≤ 0.5 subgroup [32]. Gas tamponade trials showed no consistent visual superiority; Lindtjörn, et al. reported a median gain of 3 ETDRS lines in both air and SF6 groups despite different closure rates [34].

OCT and functional outcomes were reported heterogeneously closure configuration, ELM/EZ restoration, inner retinal dimpling, dissociated optic nerve fiber layer (DONFL) appearance, retinal sensitivity, microperimetry, and OCTA measures and were not standardized. Tissue sparing approaches tended to preserve inner retinal architecture: fovea-sparing peeling preserved a thicker, smoother foveal contour and better retinal sensitivity [30], hemi-temporal peeling reduced nasal retinal migration but had lower primary closure than 360° peeling [29], and ILM repositioning reduced inner retinal dimpling and improved retinal sensitivity in one pilot trial [27]. Outer retinal restoration varied across flap trials [18,20-22,24,28].

Complications, risk of bias, and certainty of evidence

Adverse-event reporting was inconsistent. Reported complications included flap displacement, nonresolving vitreous hemorrhage, retinal detachment, cataract progression, posterior capsular opacification, transient or sustained intraocular pressure (IOP) elevation, pupillary optic capture, retinal tears or breaks, and revision surgery. Most trials were small and underpowered to compare uncommon events, no consistent safety advantage emerged for any operative modification, and interpretation was limited by incomplete complication tables and variable follow-up. Overall, 7 RCTs were at low risk of bias, 14 had some concerns, and 2 were at high risk; common issues were unclear allocation concealment, incomplete masking, post-randomization exclusions, missing outcome data, per-protocol analysis, imprecision from small sample size, and incomplete OCT or adverse-event reporting. Using a GRADE-informed approach, certainty was generally low to moderate highest for anatomical closure and lower for BCVA, OCT microstructure, complications, reoperation, and single-study adjunctive or pharmacologic interventions.

Discussion

This RCT-only systematic review found that PPV with ILM manipulation remains the principal evidence-supported management platform for FTMH, with no single universally superior intervention. Management is best interpreted according to clinical stage, OCT size, hole configuration, and chronicity, and according to the intended priority primary closure, visual recovery, tissue preservation, safety, or avoidance of reoperation. A stage-based framework is clinically useful but must be interpreted cautiously: many included trials did not report strict Gass stage and instead stratified by OCT diameter, and true stage 1 macular hole is

usually an impending or very early lesion rather than an established FTMH. The synthesis below therefore combines reported stage, OCT size, and clinical severity, and avoids assigning a trial to a stage the study did not clearly report.

Stage 1: very early or impending) macular hole

No included trial provided direct randomized evidence for true stage 1 disease. The closest pharmacological evidence topical dorzolamide in small idiopathic FTMH showed identical 8-week closure with dorzolamide and placebo (18.8% in both groups) [36], so topical carbonic anhydrase inhibitor therapy should not be presented as an evidence-based closure treatment for early FTMH; although pharmacologic vitreolysis is biologically relevant in eyes with vitreomacular traction, no eligible RCT established a stage-specific strategy. Non-surgical management is therefore largely careful observation with OCT monitoring rather than proven active treatment: in the placebo arm of Lee, et al. spontaneous closure occurred in only 3/16 small FTMHs over 8 weeks [36], supporting cautious, time-limited observation in selected early or small cases but not as definitive treatment for established symptomatic FTMH. No eligible RCT supported pneumatic vitreolysis or other office based procedures. Surgery was not studied as a separate stage 1 population, but if an early lesion progresses to a definite hole the small-hole evidence applies: conventional PPV with ILM peeling achieves high closure, more complex flap techniques add no consistent benefit over peeling [28,38], and SF6 is better supported than air for single surgery closure [34].

Stage 2: Small established FTMH

Randomized pharmacological evidence remains limited and shows no clear benefit; topical dorzolamide did not improve closure, BCVA, or early outcomes versus placebo [36], so pharmacological therapy alone should be considered unsupported for closure of established stage 2 disease. Short term, closely monitored observation may be reasonable in selected small holes when symptoms, duration, and OCT findings suggest possible spontaneous closure, but the low, identical early closure in the dorzolamide and placebo arms indicates such management should be time-limited [36]; persistent holes that underwent rescue vitrectomy all closed, supporting surgery as the more reliable option. Surgically, conventional PPV with ILM peeling is sufficient for many eyes. Ventre, et al. found 100% closure with both peeling and inverted flap and no significant final BCVA advantage for the flap [28] and SF6 improved single surgery closure versus air, though final closure and visual gains were similar after rescue [34]. Tissue-sparing approaches may reduce retinal displacement or preserve foveal architecture but can carry an anatomical trade-off: hemi-temporal peeling reduced nasal retinal migration but had lower primary

closure than 360° peeling [29], whereas fovea-sparing peeling preserved foveal contour and retinal sensitivity with high closure in selected eyes [30]. Standard ILM peeling with appropriate gas tamponade is thus the most consistent approach, with tissue-sparing techniques reserved for cases prioritizing preservation of inner retinal architecture.

Stage 3: Advanced, large, or complex FTMH

No pharmacological therapy demonstrated reliable closure benefit; dorzolamide was tested only in small holes and was ineffective [36], and PRP is better regarded as a surgical biologic adjunct than a pharmacological therapy in one pilot RCT of large holes it produced closure and BCVA similar to inverted ILM flap, with certainty limited by small sample size and short follow-up [37]. The randomized evidence does not support non-surgical management as definitive treatment for advanced holes, which are less likely to close spontaneously and more likely to require anatomical support, release of tangential traction, and tamponade; non-surgical management should therefore be limited to preoperative optimization, counseling, or brief observation when surgery is temporarily deferred.

Surgery is the dominant evidence-supported strategy, with ILM technique tailored to anatomical risk: inverted, multilayered, PFO-assisted flap, and ILM repositioning techniques may improve early closure, type 1 closure, foveal configuration, or retinal sensitivity in selected large or complex holes [18-22,27], but should not be described as universally superior because several RCTs found similar closure or BCVA versus conventional peeling or another ILM-based method [21,22,24-26,28]. Broader peeling may help when unfavorable anatomy suggests persistent tangential traction wider peeling improved closure in large holes [31] and 4-disc-diameter peeling was especially beneficial in the MHCI ≤ 0.5 subgroup [32] but more extensive peeling may induce inner retinal change, while fovea-sparing and hemi-temporal approaches better preserve tissue in selected eyes [29,30], supporting a trade-off model between anatomical strength and tissue preservation. Tamponade should likewise be individualized: SF6 was superior to air for single-surgery closure in small-to-medium holes [34], but Rishi, et al. found no clear difference among SF6, C2F6, and C3F8 in a broader stage III-IV cohort [35], so no single expansile gas is universally best for all advanced holes.

Functional recovery and OCT interpretation

Across stages, anatomical closure and functional recovery were not fully aligned; several interventions increased closure without significant between-group BCVA differences. This is clinically important because closure is necessary but not sufficient for visual recovery, which is also influenced by baseline minimum linear and base diameter, symptom duration, chronicity, cataract

progression, ELM/EZ integrity, postoperative foveal contour, inner retinal trauma, and retinal sensitivity. OCT biomarkers closure type, ELM/EZ restoration, foveal contour, inner retinal dimpling, DONFL, retinal migration, retinal sensitivity, and microperimetry deserve greater emphasis in future trials, as they may explain why interventions with similar closure rates produce different functional or structural outcomes. The current evidence suggests tissue-preserving approaches may improve some microstructural outcomes while wider peeling or flap-based approaches may improve closure in more difficult holes, but OCT reporting was too inconsistent for firm comparative conclusions.

Safety, certainty, and limitations

Complication and reoperation outcomes were inconsistently reported, limiting comparative safety conclusions. Reoperation was most clearly related to persistent nonclosure, especially in the air-tamponade arm of Lindtjörn, et al. and the hemi-temporal peeling arm of Jujo, et al. [28,34], and most trials were too small to detect uncommon adverse events such as retinal detachment, endophthalmitis, significant IOP complications, or recurrent holes. The main strengths of this review are its restriction to randomized evidence, PRISMA 2020 reporting, prospective PROSPERO registration, RoB 2 assessment, and a GRADE-informed certainty appraisal. Limitations include the restriction to PubMed/MEDLINE and to English-language RCTs (a protocol deviation that may have reduced completeness) and substantial heterogeneity in staging, size thresholds, surgical technique, tamponade, follow-up duration, OCT outcomes, and complication reporting; many trials were small, single-center, exploratory, or pilot studies, and most had some concerns or high risk of bias. These factors justify narrative synthesis over meta-analysis and warrant cautious conclusions.

Clinical implications and conclusion

For stage 1 or very early disease, direct RCT evidence is lacking: Pharmacological closure therapy is unproven, non-surgical management is mainly OCT monitoring, and surgery becomes relevant if a definite or persistent FTMH develops. For stage 2 or small established FTMH, PPV with ILM peeling and appropriate tamponade is the most consistently supported approach, SF6 is better supported than air for single-surgery closure, and tissue-sparing techniques may be considered selectively. For stage 3 or advanced/large FTMH, surgery remains the mainstay, and flap/repositioning or wider peeling may help in selected anatomically challenging holes, though no technique is universally superior. In conclusion, available randomized evidence supports PPV with ILM manipulation as the central management platform for FTMH; pharmacological and non-surgical approaches remain weakly supported or unproven

for established holes. Surgical technique should be individualized according to stage, OCT size, anatomical configuration, and the balance between maximizing closure and preserving retinal microstructure. Future RCTs should stratify patients by standardized macular-hole stage and OCT size, use intention-to-treat analysis, and consistently report primary and final closure, BCVA, ELM/EZ restoration, foveal contour, retinal sensitivity, complications, recurrence, and reoperation.

Conflicts of Interest

The authors declare no conflicts of interest.

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