AMERICAN ACADEMY OF OPHTHALMOLOGY®

The Effect of Macular Hole Duration on Surgical Outcomes

An Individual Participant Data Study of Randomized Controlled Trials

Declan C. Murphy, MBBS, MRes,[1] Mo Al-Zubaidy, MBBS, MRes,[1] Noemi Lois, PhD,[2] Neil Scott, MSc, PhD,[3] David H. Steel, MBBS, MD,[1,4] Macular Hole Duration Study Group

Topic: To define the effect of symptom duration on outcomes in people undergoing surgery for idiopathic full-thickness macular holes (iFTMHs) by means of an individual participant data (IPD) study of randomized controlled trials (RCTs). The outcomes assessed were primary iFTMH closure and postoperative best-corrected visual acuity (BCVA).

Clinical Relevance: Idiopathic full-thickness macular holes are visually disabling with a prevalence of up to 0.5%. Untreated BCVA is typically reduced to 20/200. Surgery can close holes and improve vision. Symptom duration is thought to affect outcomes with surgery, but the effect is unclear.

Methods: A systematic review identified eligible RCTs that included adults with iFTMH undergoing vitrectomy with gas tamponade in which symptom duration, primary iFTMH closure, and postoperative BCVA were recorded. Bibliographic databases were searched for articles published between 2000 and 2020. Individual participant data were requested from eligible studies.

Results: Twenty eligible RCTs were identified. Data were requested from all studies and obtained from 12, representing 940 eyes in total. Median symptom duration was 6 months (interquartile range, 3−10). Primary closure was achieved in 81.5% of eyes. There was a linear relationship between predicted probability of closure and symptom duration. Multilevel logistic regression showed each additional month of duration was associated with 0.965 times lower odds of closure (95% confidence interval [CI], 0.935−0.996, $P = 0.026$). Internal limiting membrane (ILM) peeling, ILM flap use, better preoperative BCVA, face-down positioning, and smaller iFTMH size were associated with increased odds of primary closure. Median postoperative BCVA in eyes achieving primary closure was 0.48 logarithm of the minimum angle of resolution (logMAR) (20/60). Multilevel logistic regression showed for eyes achieving primary iFTMH closure, each additional month of symptom duration was associated with worsening BCVA by 0.008 logMAR units (95% CI, 0.005−0.011, $P < 0.001$) (i.e., ∼1 Early Treatment Diabetic Retinopathy Study letter loss per 2 months). ILM flaps, intraocular tamponade using long-acting gas, better preoperative BCVA, smaller iFTMH size, and phakic status were also associated with improved postoperative BCVA.

Conclusions: Symptom duration was independently associated with both anatomic and visual outcomes in persons undergoing surgery for iFTMH. Time to surgery should be minimized and care pathways designed to enable this. *Ophthalmology 2022;■:1−12 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.aaojournal.org.

An idiopathic full-thickness macular hole (iFTMH) is a common and visually disabling retinal disorder. They occur bilaterally in 10% of cases. The overall incidence is approximately 4 to 8 per 100 000 per annum, which increases to approximately 30 per 100 000 in women aged 60 to 70 years.[1,2] If left untreated, iFTMHs lead to a reduction in best-corrected visual acuity (BCVA), typically at less than 20/200 (Snellen), and are an important cause of visual morbidity.[3]

There are 2 main outcomes that indicate surgical success after surgery to treat IFTMHs: iFTMH hole closure and final postoperative vision. For iFTMHs with a minimum linear diameter (MLD) measurement less than 500 μm, primary hole closure occurs in 85% to 95% of cases; as the size of the hole increases, the rates of hole closure decrease.[4] The visual acuity (VA) achieved after surgery with successful hole closure is variable; approximately 60% gain at least 0.3 logarithm of the minimum angle of resolution

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(logMAR) units, but only 35% to 40% achieve vision sufficient to legally allow them to drive a motorized vehicle in the United Kingdom (20/40).[5]

Several factors have been proposed to affect both postoperative hole closure and vision, most notably iFTMH size. Preoperative BCVA is also known to be highly correlated with postoperative vision after successful hole closure.[6] The length of time a hole has been present before surgery, typically estimated by the symptom duration, termed the "duration" in this article, is also thought to affect both postoperative hole closure and vision.

To date, there have been no prospective studies specifically designed to investigate the effects of symptom duration on iFTMH outcomes after surgery. Published literature shows that the current evidence of the link between duration and iFTMH closure and postoperative vision is variable. Some studies, including 3 that used large databases, suggest an association between duration and postoperative hole closure and BCVA.[7–11] At least 5 other studies investigating different treatments for iFTMHs, including 1 randomized controlled trial (RCT), found no effect.[12–16] However, these studies have several important limitations, which include inaccurate recordings of VA, for example, using recordings that were performed at variable time points before and after surgery, as well as inconsistent methods and timing to measure iFTMH sizes before surgery, the confounding effects of cataract formation, and differing definitions of duration. These limit the reliability of conclusions derived from these studies.

Duration is associated with both iFTMH size and preoperative VA; with time, the hole enlarges and vision deteriorates. This association both enhances the effect of duration and confounds studies that aim to analyze the effect of duration on outcomes. Understanding exactly how duration affects anatomic and functional outcomes after vitreoretinal surgery is important because it is a potentially modifiable variable.

In this study, we aimed to investigate the effect of hole duration on surgical outcomes after iFTMH surgery using individual participant data (IPD) obtained from previously published RCTs presenting surgical outcomes of FTMHs that included data on symptom duration. We obtained IPD from RCTs for the purpose of the analysis presented because this study design would be most likely to guarantee that the methodology used for data collection was of high quality and robust. Relevant literature was identified by performing a comprehensive Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant systematic search of relevant RCTs.

Methods

We first performed a PRISMA-compliant systematic review methodology of published scientific literature to identify eligible RCTs (Supplementary Material 1, available at www.aaojournal.org). A systematic review study protocol was prospectively registered on PROSPERO database (CRD42020200664). We performed the systematic review search strategy in accordance with the methodological processes outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[17] and the PRISMA statement.[18]

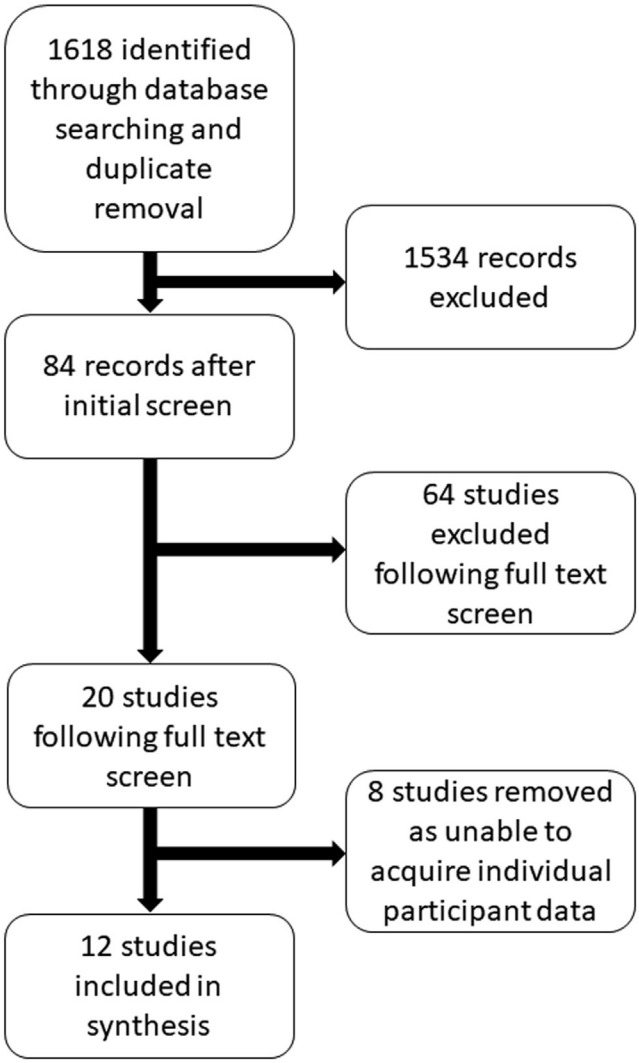

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant flowchart that shows the number of studies identified following the search strategy. It demonstrates the points at which exclusions were made and how the final 12 relevant studies were chosen for analysis.

A prospective comprehensive search strategy was developed using appropriate free-text and MeSH terms with variations of key words connected with Boolean operator terms. The following electronic bibliographic databases were searched: Ovid (MEDLINE), Ovid (Embase), Cochrane Library, Health Management Information Consortium, Web of Knowledge, Scopus, and trial registers (ClinicalTrials.gov, World Health Organization International clinical trials registry platform) (Supplementary Material 2, available at www.aaojournal.org). Reference lists of eligible studies and previously published review articles were also searched to identify other potentially eligible studies that may have been missed by the search strategy. All peer-reviewed literature published in the English language between January 2000 and August 2020 were considered.

Inclusion and exclusion criteria were prospectively defined. We included all randomized controlled trials (RCTs) that included

Table 1. All Studies Included in Individual Participant Data Analysis

Study (Primary Author, Published Date)	Funder	Eyes/Patients per Study (N)	Country	Study's Primary Investigation	Included iFTMH Sizes (μm)	Maximum Symptom Duration (mo)	Intraocular Tamponade Agent	Lens Management	pPH or PhV at Baseline (N)	Postoperative Positioning Instructions	Type of ILM Staining Dye Used	Postoperative Time-points (mos)	Visual Acuity Method†
Yao et al, 2018,	Beijing Municipal Science and Technology Commission; National Natural Science Foundation of China Grant	121/121	China	ILM peeling	All sizes	<36	20% SF6	PhV allowed	1 pPH; 102 PhV	FDP 14 days	ICG	3, 6, 12	Refraction/ETDRS
Velez-Montoya et al, 2018	Departmental funds only	38/38	Mexico	ILM flap	>400 μm	<12	18% SF6 or 14% C3F8	PhV allowed	4 pPH; 6 PhV	FDP 3 days	BBG	3	BCVA/Snellen
Pasu et al, 2020	NIHR Research for Patient Benefit grant (PB-PG-0213-30085)	178/178	UK	FDP	>400 μm	<12	14% C3F8	PhV allowed	28 pPH; 89 PhV	Randomized	TB and BBG	3	BCVA/ETDRS
Yorston et al, 2012	Departmental funds only	30/30	UK	FDP	All sizes	<12	14% C3F8	All PhV	All Phakic	Randomized	TB and BBG	6	Refraction/Snellen
Lange et al, 2012	NIHR departmental support	30/30	UK	FDP	All sizes	<12	14% C3F8	No PhV	All Phakic	Randomized	BBG	3	BCVA/Snellen
Manasa et al, 2018	Departmental funds only	91/91	India	ILM flap	>600 μm	<36	20% SF6	All pPH	All pPH	FDP 3 days	BBG	3	BCVA/ETDRS
Michalewska et al, 2010	Departmental funds only	101/86	Poland	ILM flap	>400 μm	<42	Air	No PhV	6 pPH	FDP 4 days	TB	3, 6,12	BCVA/Snellen
Alberti, 2016	Synoptik Foundation, Copenhagen; Fight for Sight Denmark, Copenhagen	68/68	Denmark	FDP	All sizes	<24	15% C3F8	All Ph preoperatively	All pPH	Randomized	BBG	3	BCVA/ETDRS
Christensen et al, 2008	The Danish Eye Health Society; The Danish Medical Research Council; The John and Birthe Meyer Foundation; The Velux Foundation.	89/89	Denmark	ILM peeling	All sizes	<12	15% C3F8	All Ph preoperative	All pPH	FDP 5 days	ICG and TB	3, 6, 12	BCVA/ETDRS
Lois et al, 2011	Chief Scientist Office, Scotland	138/138	UK	ILM peeling	All sizes	<18	12% C3F8	All PhV	7 pPH; 131 PhV	FDP 5–7 days	TB	3, 6	Refraction/ETDRS
Kwok et al, 2005	Departmental funds only	51/49	China	ILM peeling	All sizes	<24	12% C3F8	PhV allowed	1 pPH; 28 PhV	FDP 14 days	ICG	6 to 23	Refraction/Snellen
Briand et al, 2015*	Departmental funds only	59/59	Canada	Gas type	All sizes	<12	20% SF6 or 15% C3F8	PhV allowed	8 pPH; 6 PhV	FDP 7–14 days	TB and ICG	3, 6, 12	BCVA/ETDRS

Key descriptive characteristics of the included randomized controlled trial studies included in the individualized participant data analysis.
BBG = Brilliant Blue G; BCVA = best-corrected visual acuity; C3F8 = octafluoropropane; ETDRS = Early Treatment Diabetic Retinopathy Study; FDP = face-down positioning; ICG = indocyanine green; iFTMH = idiopathic full-thickness macular hole; ILM = internal limiting membrane; N/A = not available; NIHR = National Institute for Health and Care Research; Ph = phacoemulsification; PhV = combined phacovitrectomy; pPH = pseudophakic; SF6 = sulfur hexafluoride; TB = trypan blue.
*Briand et al recorded time from diagnosis to surgery rather than symptom duration.
†Protocol-based refracted visual acuity (VA) versus BCVA with method unclear/recording chart used; Snellen or ETDRS chart at 4 m.

Table 2. Baseline Characteristics of Included Studies

Study	No. of Eyes Included	ILM Peel, n (%)	ILM Flap, n (%)	Age, yrs (Median, Range)	MLD, μm (Median, Range)	Duration, mos (Median, Range)	Preoperative BCVA, logMAR (Median, Range)
Yao et al, 2018	121	121 (100)	0 (0)	65 (45–78)	468 (127–1050)	2 (0.25–36)	0.78 (0.22–1.4)
Velez-Montoya et al, 2018	38	38 (100)	27 (71)	62.5 (32–76)	590.5 (380–922)	3 (1–12)	1 (0.17–1.7)
Pasu et al, 2020	184	184 (100)	0 (0)	69 (46–84)	482.5 (42–854)	7 (0–12)	1 (0.3–3)
Yorston et al, 2012	30	30 (100)	0 (0)	69 (57–81)	380 (20–670)	7.5 (4–15)	0.975 (0.5–1.6)
Lange et al, 2012	30	30 (100)	0 (0)	69.5 (50–79)	446.5 (150–1085)	6 (2–11)	0.97 (0.17–1.12)
Manasa et al, 2018	91	91 (100)	43 (47)	62 (42–83)	666 (62–1481)	12 (1–36)	1 (0.48–1.78)
Michalewska et al, 2010	86	86 (100)	46 (53)	67 (48–78)	671.5 (405–1618)	17 (6–60)	1 (0.52–2)
Alberti, 2016	68	68 (100)	0 (0)	70 (48–82)	405.5 (70–688)	7.1 (4–24)	0.7 (0.24–1)
Christensen et al, 2008	47	26 (55)	0 (0)	66 (57–78)	424 (199–760)	8 (2–12)	0.66 (0.52–0.96)
Lois et al, 2011	137	71 (51)	0 (0)	70.5 (54–87)	420 (92–761)	6 (1–24)	0.68 (0.26–1.7)
Kwok et al, 2005	49	26 (53)	0 (0)	65 (38–78)	500 (150–1000)	11 (2–72)	1 (0.3–1.3)
Briand et al, 2015	59	59 (100)	0 (0)	69 (51–83)	412.5 (24–748)	2.73 (0.03–6.87)	0.92 (0.62–1.64)
Combined dataset	940	830 (88)	116 (12)	68 (32–87)	492 (20–1618)	6 (0–72)	0.84 (0.17–3)

BCVA = best-corrected visual acuity; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MLD = minimum linear diameter.

adult (≥ 18 years) participants with an iFTMH who underwent vitrectomy surgery with gas or air tamponade in association with any of the following maneuvers: internal limiting membrane (ILM) peeling of any size or type, ILM flap, cataract surgery, any type of staining for ILM (or associated epiretinal membrane), and any type of postoperative positioning protocol. We only included RCTs in which the duration of symptoms from onset to the time of the surgery or iFTMH duration from diagnosis to the time of the surgery was available and RCTs in which the dimensions (at least including MLD) of the iFTMH had been recorded.

We excluded RCTs that investigated secondary macular holes, including those that developed in association with trauma, retinal detachment, myopia > 6 diopters, or retinal dystrophies. Likewise, we excluded RCTs investigating macular holes treated with silicone oil tamponade, eyes with iFTMH that had failed prior interventions, and holes in people with other pathologies affecting their visual function (e.g., amblyopia, optic neuropathies, advanced age-related macular degeneration, and diabetic macular edema). We excluded all studies that were not RCTs.

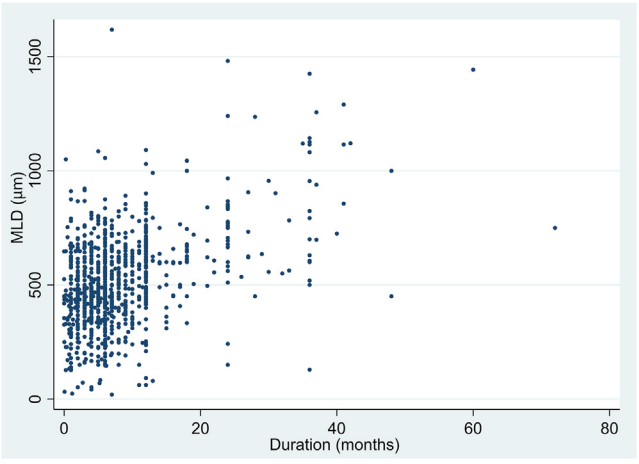

Figure 2. A scatter graph showing idiopathic full-thickness macular hole (iFTMH) symptom duration plotted against iFTMH size (defined by measuring the minimum linear diameter [MLD]). There was a positive correlation between duration and MLD. There was large variability in MLD for individuals with short symptom durations.

Two investigators (D.C.M. and M.A.) independently screened studies that were obtained from the search strategy. First, studies were screened according to their title and abstract and were classified as potentially eligible or ineligible. Disagreements were resolved by discussion or with intervention of a third reviewer (D.H.S.), who arbitrated if required, until consensus was agreed. Full text articles for all potentially eligible studies were acquired and reviewed independently by D.C.M. and M.A. to determine their eligibility. Likewise, any disagreements were resolved by discussion with D.C.M. and M.A. and D.H.S. if necessary.

For those considered eligible for inclusion, we requested IPD from the corresponding authors by email. We allowed the corresponding author 2 months to reply to our email correspondence in total. If no reply was received after 4 weeks, we sent a second email. We included only studies in which IPD was provided. Included studies were pooled into a single dataset and recoded using a standard coding sheet. Only 1 eye per patient was included in the IPD, and in studies that included participants who had undergone iFTMH surgery to both eyes, we included data corresponding to the eye that first underwent surgery only.

Because we used data from RCTs for a different reason to their original research question, it was not appropriate to use typical risk of bias assessments for the studies. Rather, to assess the quality of the included studies and their risk of bias, we used the Quality in Prognosis Studies (QUIPS) tool; this is a tool that has been used in other IPD analyses of studies investigating prognostic indicators.[19–21] For the assessment, 6 domains were scored: representativeness of study population, adequateness of follow-up period and attrition, study variable measurements, outcome measurements, adequateness of statistical analysis and reporting, and conflict of interests. For each of these 6 domains, the responses "yes," "partial," "no," or "unsure" for 3 up to 7 items within each domain are combined to assess the risk of bias. An overall rating for each domain is assigned as "high," "moderate," or "low" risk of bias. The QUIPS assessment for each study was independently completed by 2 observers, with agreement reached by consensus in cases of disagreement. A study was considered to be of low risk of bias when the items were rated as low or moderate on all of the 6 domains, with at least 4 rated as low (of which the outcome

Table 3. Idiopathic Full-Thickness Macular Hole Size and Postoperative Best-Corrected Visual Acuity

Duration (mos)	iFTMH Size (MLD) in μm Mean (SD) [N]	Postoperative BCVA in logMAR Units (Snellen Equivalent) Mean (SD) [N]
0–6	461.4 (163) [412]	0.459 (20/58) (0.272) [411]
>6–12	502.0 (182) [208]	0.511 (20/65) (0.328) [211]
>12	680.2 (272) [77]	0.838 (20/138) (0.391) [76]

Demonstration of iFTMH size and postoperative BCVA relative to symptom duration in months. As duration increases in length, so does iFTMH size and logMAR units (worsening vision).
BCVA = best-corrected visual acuity; iFTMH = idiopathic full-thickness macular hole; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MLD = minimum linear diameter; SD = standard deviation.

measurement domain must be rated as low at least). A study was scored as high risk of bias if 2 or more of the domains were scored as high. The remaining studies were scored as moderate.[22]

We investigated the effect of symptom duration on 2 surgical outcomes: primary anatomic closure of the iFTMH (i.e., surgical closure after first surgery) and BCVA at 6 months postoperatively. If postoperative BCVA data were not available at 6 months, we used the nearest available time. The difference between preoperative BCVA and postoperative BCVA was included as a secondary end point. All VA measurements were converted to logMAR units for analysis. Missing, invalid, out-of-range, or inconsistent data entries were queried with the corresponding authors of included trials. We asked all studies to send the hole size as MLD, as defined by the International Vitreomacular Traction Study Group classification.[23]

To assess the overall certainty of the evidence, we used a modified Grades of Recommendation, Assessment, Development, and Evaluation approach that defines quality of evidence as confidence in effect estimates, modified to assess evidence about prognosis.[24] The methodology considers study design (randomized trials vs. nonrandomized designs), risk of bias, inconsistency, imprecision, indirectness, and publication bias; size and trend in the effect are also considered. Ethical approval to undertake this study was obtained from the London Bridge Research Ethics Committee (Reference 20/PR/0406). All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

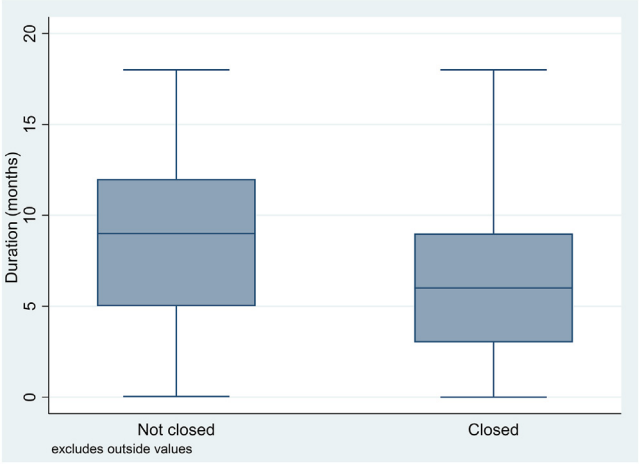

Figure 3. Median duration of symptoms in those who achieved iFTMH closure after a single surgical operation compared with those who did not. Box plots show that median duration was lower for those who achieved primary closure compared with those who did not (6 months [IQR, 3–9; n = 759] and 9 months [IQR, 5–12; n = 173], respectively). iFTMH = idiopathic full-thickness macular hole; IQR = interquartile range; n = number.

Statistical Analysis

Descriptive data were presented using appropriate tabular and graphical summaries. A multilevel logistic regression model was used to examine factors associated with primary closure of the iFTMH. Studies were included as random effects in the model, and results were adjusted for age, surgical variables including ILM peeling (yes/no), ILM flaps (yes/no), the use of other intraoperative adjuvants (yes/no), the use of indocyanine green staining (yes/no), the type of gaseous tamponade used, preoperative BCVA, postoperative face-down positioning, MLD size, and phakic status. We classified phakic status as follows: (1) pseudophakic (at baseline)/pseudophakic (at follow-up time point chosen for VA analysis) (reference category); (2) phakic preoperatively and postoperatively at the time point used for BCVA measurement; and (3) phakic preoperatively and pseudophakic at the time-point chosen for measuring BCVA. We expressed results using odds ratios (ORs) and their 95% confidence intervals (CIs). The model was then used to estimate predicted probabilities of hole closure with 95% CIs for combinations of iFTMH duration, iFTMH size, and preoperative BCVA.

A similar multilevel regression model examined the effect of duration on postoperative BCVA for those with primary iFTMH closure while adjusting for the same aforementioned covariates.

Additional analyses were conducted to investigate the effect of duration on postoperative BCVA for all patients and the effect of duration on change in BCVA from baseline for all patients and for those who achieved successful postoperative iFTMH closure. Another analysis investigated the effect of duration on achieving a postoperative BCVA of logMAR $\geq$ 0.3.

A sensitivity analysis investigated the effect of excluding the study by Briand et al[25] on the primary outcomes, because they defined "duration" as the time from diagnosis to surgery, which was different than how all other studies defined it (duration of symptoms before surgery). Two further sensitivity analyses used interaction terms to explore whether pairs of predictors showed a nonlinear effect on the primary outcomes. The relationship between duration and iFTMH postoperative hole closure and the relationship between hole size and closure were tabulated.

Results

We identified 20 eligible RCTs.[15,25–43] We attempted to contact all corresponding authors via email and requires IPD from their study

Table 4. Proportion of iFTMHs Achieving Primary Closure According to Duration

Duration	Proportion with Primary Closure of the iFTMH, N (%)
0–3 mos	211/239 (88.3%)
>3–6 mos	253/296 (85.5%)
>6–12 mos	218/279 (78.1%)
>12–24 mos	46/76 (60.5%)
>24–72 mos	31/42 (73.8%)

The proportion of eyes that achieved closure of their iFTMH after a single surgery (defined as primary closure) according to symptom duration (subdivided according to specific symptom duration time bands. Overall, as duration increases, the rates of primary closure decrease.
iFTMH = idiopathic full-thickness macular hole.

participants. In total, 12 studies provided IPD that represented 940 eyes.[25,28,33–37,40–44]

All authors who replied were willing to share data. The only studies not included were those for which we received no response from the corresponding author (Fig 1).

Population and Study Characteristics

Details of the 12 RCTs included in the analysis are displayed in Table 1, and their baseline characteristics are shown in Table 2.

The median (interquartile range [IQR]) age was 68 years (IQR, 63–72), and duration of symptoms at the time of surgery was 6 (IQR, 3–10) months. Symptom duration was 0 to 3 months in 239 eyes (25.6%), 3 to 6 months in 296 eyes (31.8%), 6 to 12 months in 279 eyes (29.9%), 12 to 24 months in 76 eyes (8.2%), and 24 to 72 months in 42 eyes (4.5%).

The median MLD was 492 μm (400–624), and preoperative BCVA was 0.84 logMAR (Snellen equivalent: 20/138). Eighty-eight percent underwent ILM peeling, and an ILM flap was performed in 12% of cases.

Details of the trials for which we could not obtain IPD and that were therefore not included are shown in Supplementary Material 3 and 4 (available at www.aaojournal.org).

Relationship among Hole Size, Baseline VA, and Duration

The relationship between duration and iFTMH hole size is displayed in Figure 2. Overall, there was a positive correlation between hole size and symptom duration; larger hole sizes had longer durations. Hole size was highly variable for those with short symptom durations. There was also a similar reduction in BCVA associated with increasing iFTMH duration (Table 3).

Effect of Duration on Anatomic Closure

Postoperative iFTMH closure after the first surgical intervention (termed "primary closure") was achieved in 761 of 934 eyes (81.5%). The median duration of symptoms for those with primary closure was 6 months (IQR, 3–9; n = 759) and for those without primary hole closure was 9 months (IQR 5–12; n = 173) (Fig 3). The rates of primary iFTMH closure according to duration, subdivided into specific categories, are presented in Table 4. The relationship between the predicted probability of closure and the symptom duration was linear (Fig 4).

To illustrate the effects of duration on hole closure, we have developed a table containing predicted probabilities for iFTMH primary closure that compare 5 iFTMH sizes (MLD measurements 200 μm, 300 μm, 450 μm, 600 μm, and 800 μm) with 3 specific preoperative visual acuities of logMAR 0.48 (Snellen equivalent: 20/60), logMAR 1 (Snellen equivalent: 20/200), and logMAR 1.3 (Snellen equivalent: 20/400) for individuals with symptom durations of 6 and 18 months (Supplementary Material 5, available at www.aaojournal.org).

The results of the model predicting iFTMH hole closure are shown in Table 5. The multilevel logistic regression model suggested that each additional month of duration was associated with an odds of iFTMH closure that was 0.965 times lower (95% CI, 0.935–0.996, $P = 0.026$). Other variables associated with greater odds of iFTMH closure included ILM peeling, the use of ILM flaps during surgery, better preoperative BCVA, postoperative face-down positioning, and a smaller size hole (MLD). When predicting iFTMH closure, 1 additional month of symptom duration was approximately equivalent in effect to an additional 10 μm of MLD size.

Postoperative Vision Outcomes

The median postoperative BCVA at 6 months follow-up was 0.5 logMAR (Snellen equivalent: 20/63) (IQR, 0.3–0.78) (N = 914). The median postoperative BCVA for eyes after primary hole closure (n = 747) was 0.48 logMAR (Snellen equivalent: 20/60) (IQR, 0.3–0.7). The relationship between symptom duration and postoperative visual outcomes is shown in Figure 5.

The outputs from a multilevel linear regression model predicting postoperative BCVA for eyes with successful primary IFTMH closure based on relevant preoperative variables are shown in Table 6. Each additional month of duration was associated with an increase in 0.008 logMAR units (95% CI, 0.005–0.011, $P < 0.001$) for postoperative BCVA at 6 months (i.e., VA deteriorates). This means that for every 10 months of extra duration, independent of hole size increase or preoperative VA reduction during that time, there was a decrease of approximately 1 line of Snellen acuity in postoperative BCVA (e.g., 20/40 to 20/32). The intraoperative use of ILM flaps, long-acting gas tamponade, better preoperative BCVA, smaller hole size (MLD), and phakic status were associated with improved postoperative BCVA. When considering BCVA at 6 months follow-up, each additional month of symptom duration is approximately equivalent to 40 μm of iFTMH size (MLD).

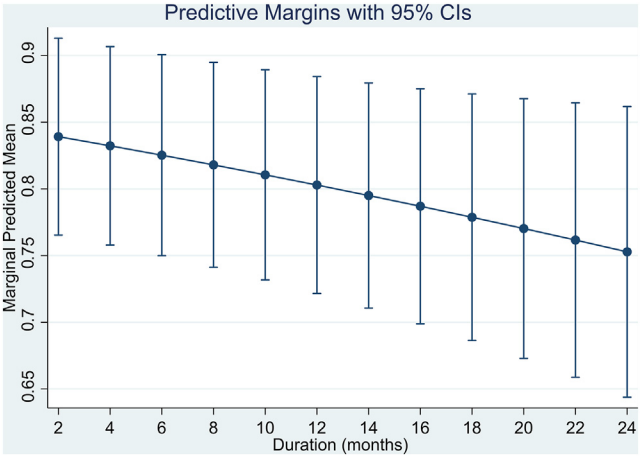

Figure 4. Dot plot of predicted probability of iFTMH primary closure according to symptom duration. As duration increases, the predicted probability of primary closure decreases. CI = confidence interval; iFTMH = idiopathic full-thickness macular hole.

Table 5. Results from a Multilevel Logistic Regression Model Predicting Idiopathic Full-Thickness Macular Hole Closure

	Odds Ratio	95% CI	*P* Value
Duration (mos)	0.965	(0.935−0.996)	0.026*
Age (yrs)	1.017	(0.986−1.048)	0.287
ILM peeling	18.16	(8.14−40.47)	<0.001*
ILM flaps	3.656	(1.673−7.988)	0.001*
ICG dye	1.676	(0.473−5.930)	0.423
Long-acting gas	1.061	(0.281−4.014)	0.930
Preoperative BCVA (logMAR)	0.387	(0.192−0.777)	0.008*
Face-down positioning	2.884	(1.172−7.094)	0.021*
MLD (μm)	0.996	(0.994−0.997)	<0.001*
Phakic/phakic	1.712	(0.651−4.501)	0.276
Phakic/pseudophakic	1.711	(0.666−4.399)	0.265

Results are based on N = 915. Duration, ILM peeling, ILM flaps, preoperative BCVA, face-down positioning, and MLD were significant predictors of hole closure.
BCVA = best-corrected visual acuity; CI = confidence interval; ICG = indocyanine green; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MLD = minimum linear diameter.
*Statistically significant results ($P \leq 0.05$).

Models with Interaction Terms

For the 2 primary outcomes, 3 additional interaction terms for each pairwise combination of duration, hole size, and preoperative VA were added to the model to investigate whether any combination of these variables had a nonlinear effect on the probability of hole closure or postoperative BCVA. In each case, no interaction term was statistically significant ($P > 0.05$ for all), suggesting that the effect of duration on hole closure and postoperative VA is linear.

Sensitivity Analysis with Exclusion

Briand et al[25] defined "duration" as the time from diagnosis to surgery, rather than the duration of symptoms, which is how every other study defined it, as the other studies did. To assess whether this affected the results, we analyzed the data after excluding the study by Briand et al.[25] The results were similar. An additional month of duration of the iFTMH was associated with odds of primary closure of 0.964 (95% CI, 0.934−0.996) ($P = 0.026$, n = 857) and increased postoperative logMAR of 0.008 (95% CI, 0.005−0.011) ($P < 0.001$, n = 685).

Secondary Analyses

Symptom duration had a similar effect on postoperative BCVA when the analysis included both patients who achieved iFTMH closure and those who did not (Supplementary Material 6, available at www.aaojournal.org).

When examining the change in VA from baseline, a longer duration of the iFTMH was associated with worse vision outcomes (Table 7). Duration was also found to predict whether patients achieved a postoperative BCVA of 0.3 or better (OR, 0.065, $P = 0.006$), as were preoperative VA (OR, 2.848, $P < 0.001$) and MLD (OR, 0.003, $P = 0.001$) (Table 8).

Study Quality and Risk of Bias

The QUIPS tool was used to examine the risk of bias for all included studies.[21] Nine of the 12 studies were judged at low risk of bias overall, and 3 were judged at moderate risk. None were considered at high risk of bias (Fig 6).

Overall Certainty of Evidence

Using a modified Grades of Recommendation, Assessment, Development, and Evaluation approach, as detailed in the "Methods," we graded the overall certainly of evidence for the included studies as moderate (Fig 6).

Discussion

This IPD meta-analysis of RCTs, which included 940 eyes of 940 patients, showed that symptom duration before iFTMH surgery is strongly and consistently associated with poorer anatomic (i.e., lower rates of hole closure) and visual outcomes (i.e., less BCVA improvement after surgery and lower final postoperative vision) after surgery. The effect was independent of preoperative hole size and VA. The effect is linear and begins from symptom onset. Its effect size is significant and clinically important.

We used the data of individual participants from RCTs to ensure the quality and accuracy of the data. Seventy-five percent of the RCTs were graded as having a low risk of bias and non−high risk, adding to the validity of our findings. In our analyses, we controlled for a range of variables that could affect anatomic and visual outcomes. As a result, we confirmed that ILM peeling improves hole closure, as does the use of ILM flaps intraoperatively and postoperative face-down positioning. In addition, we showed that postoperative vision is improved after the use of ILM flaps and long-acting gas for tamponade.

Patients with iFTMHs can present with varying signs and symptoms. Their symptom duration and extent of VA loss, and the size of their hole can be highly variable. In our study, we found all 3 characteristics were interrelated (i.e., a longer duration was associated with a larger hole size and worse VA at presentation); however, each was also independently

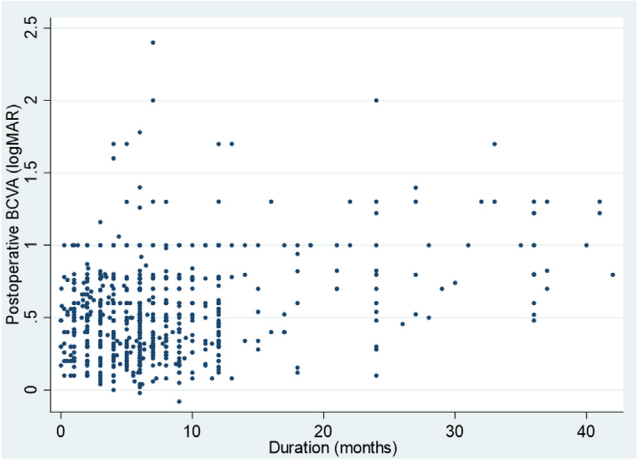

Figure 5. Scatter graph showing the association between symptom duration and BCVA 6 months after successful surgery. As symptom duration increases, postoperative vision worsens (increase in logMAR units). BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

Table 6. Multilevel Linear Regression to Predict Postoperative BCVA at 6 Months after Successful Primary Hole Closure

	Coefficient	95% CI	P Value
Duration (mos)	0.008	(0.005–0.011)	<0.001*
Age (yrs)	0.002	(−0.001 to 0.005)	0.165
ILM peeling	−0.016	(−0.106 to 0.073)	0.719
ILM flaps	−0.092	(−0.166 to −0.175)	0.016*
ICG dye	−0.038	(−0.119 to 0.044)	0.364
Long-acting gas	−0.997	(−0.184 to −0.015)	0.021*
Preoperative BCVA (logMAR)	0.366	(0.302–0.430)	<0.001*
Face-down positioning	−0.020	(−0.075 to 0.035)	0.471
MLD (μm)	0.0002	(0.0001–0.0004)	<0.001*
Phakic/phakic	0.108	(0.038–0.178)	0.003*
Phakic/pseudophakic	0.062	(−0.006 to 0.129)	0.072

A multilevel linear regression model was performed to predict postoperative BCVA (logMAR) at 6 months follow-up for individuals who achieved successful primary IFTMH closure. Calculations are based on a sample of N = 731. Duration, ILM flaps, long-acting gas, preoperative BCVA, MLD, and phakic/phakic status before and after surgery were significant predictors of BCVA.
BCVA = best-corrected visual acuity; CI = confidence interval; ICG = indocyanine green; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MLD = minimum linear diameter.
*Statistically significant results ($P \leq 0.05$).

Table 7. Multilevel Linear Regression Models Predicting Change in BCVA for all Patients (N = 897) and for Those Who Achieved Primary iFTMH Closure (N = 731)

Change in BCVA (logMAR) for All Patients (N = 897)			
	Coefficient	*95% CI*	*P Value*
Duration (mos)	0.005	(0.002–0.008)	0.002*
Age (yrs)	0.001	(−0.002 to 0.004)	0.683
ILM peeling	−0.103	(−0.187 to −0.018)	0.017*
ILM flaps	−0.133	(−0.217 to −0.048)	0.002*
ICG dye	−0.012	(−0.113 to 0.089)	0.814
Long-acting gas	−0.075	(−0.184 to 0.034)	0.178
Face-down positioning	−0.090	(−0.159 to −0.020)	0.011*
MLD (μm)	0.0001	(−0.0001 to 0.0002)	0.398
Phakic/phakic	0.043	(−0.044 to 0.130)	0.335
Phakic/pseudophakic	0.040	(−0.044 to 0.125)	0.350
Change in BCVA (logMAR) after Primary Hole Closure (N = 731)			
	Coefficient	*95% CI*	*P Value*
Duration (mos)	0.005	(0.001–0.009)	0.009*
Age (yrs)	0.001	(−0.002 to 0.005)	0.383
ILM peeling	−0.095	(−0.204 to 0.014)	0.088
ILM flaps	−0.118	(−0.209 to −0.027)	0.011*
ICG dye	−0.037	(−0.131 to 0.057)	0.440
Long-acting gas	−0.089	(−0.185 to 0.008)	0.072
Face-down positioning	−0.013	(−0.080 to 0.055)	0.713
MLD (μm)	0.0000	(−0.0002 to 0.0001)	0.400
Phakic/phakic	0.053	(−0.030 to 0.136)	0.209
Phakic/pseudophakic	0.041	(−0.039 to 0.120)	0.314

Multilevel linear regression was performed to predict change in BCVA after surgery for all patents (calculations based on N = 897) and for patients who achieved primary hole closure (calculations based on N = 731). For both, duration was a significant positive predictor for postoperative BCVA (logMAR units, i.e., worse vision).
BCVA = best-corrected visual acuity; CI = confidence interval; ICG = indocyanine green; iFTMH = idiopathic full-thickness macular hole; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MLD = minimum linear diameter.
*Statistically significant results ($P \leq 0.05$).

associated with anatomic and visual outcomes. The size of the iFTMH at presentation was variable, with some being larger despite having a short duration of symptoms. This may relate partly to the person affected being unaware of the problem, and thus presenting late especially if it is the nondominant eye affected, for example. It may also relate to anatomic characteristics, including foveal floor and vitreomacular traction width, both of which are known to vary between individuals and differ according to ethnicity.[45,46] The rate by which an iFTMH enlarges also depends on the presenting size; smaller holes grow faster than larger holes.[47,48] The effect of hole size and duration on postoperative outcomes was independent, with the effect being additive, which means the prognosis of small holes will worsen more with time than that of larger holes; this is related to their greater concomitant size increase and visual decline before surgery. To illustrate this, a person presenting with a 200 μm iFTMH and 0.48 logMAR preoperative BCVA with a 6-month history of symptoms that increases to 400 μm and 1.0 logMAR at 18 months has a change in predicted closure rate from 0.94 to 0.83, a decrease of 11% in absolute risk and an approximately 300% relative increased risk of nonclosure. Although the spontaneous closure rate in smaller holes is likely to be higher than previously stated, it is not a common observation, and delaying surgery on the basis that they may spontaneously close carries a risk of a worsened prognosis after surgery. On the basis of the results of the current study, we advocate prompt referral and surgery for all primary macular holes, especially small ones, as the best means of achieving macular hole closure and good final functional results.[4,49]

The length of time a macular hole has been present before surgery can be divided into 3 components: (1) the symptom duration at first presentation to any care provider; (2) the time spent in a care pathway prior for the patient to have a diagnosis of the iFTMH confirmed, having been evaluated by vitreoretinal surgeon; and (3) any waiting time from diagnosis to surgery. All 3 will vary widely by population and healthcare system. A UK database study found that the median total duration of macular holes was 4 months at presentation, with 7% being more than 12 months. During the severe acute respiratory syndrome coronavirus 2 pandemic in the United Kingdom, iFTMH surgery was not prioritized, and anecdotally, waiting times have significantly increased.[50] This study has shown the importance of duration of the iFTMH on postoperative anatomic and visual outcomes and supports the development of prioritization care pathways for people with this condition to ensure early suspicion (e.g., through increasing public awareness) and prompt diagnosis and treatment (e.g., with effective healthcare pathways that allow shortening the time between diagnosis and surgery).

In addition to the benefits of early surgery for patients with iFTMHs, the results of this study suggest other

Table 8. Multilevel Logistic Regression Model Predicting BCVA of 0.3 logMAR or Better for All Patients Who Achieved Primary iFTMH

	Odds Ratio	95% CI	*P* Value
Duration (mos)	0.065	(0.018–0.111)	0.006*
Age (yrs)	0.017	(−0.010 to 0.043)	0.212
ILM peeling	−0.268	(−0.922 to 0.385)	0.421
ILM flaps	−0.319	(−1.510 to 0.872)	0.600
ICG dye	0.019	(−0.831 to 0.869)	0.965
Long-acting gas	−0.996	(−2.023 to 0.031)	0.057
Preoperative VA (logMAR)	2.848	(1.942 to 3.753)	<0.001*
Face-down positioning	−0.190	(−0.710 to 0.329)	0.473
MLD (μm)	0.003	(0.002–0.004)	<0.001*
Phakic/phakic	0.415	(−0.359 to 1.189)	0.293
Phakic/pseudophakic	0.217	(−0.491 to 0.924)	0.549

Multilevel logistic regression was performed to predict patients who achieved a BCVA of 0.3 logMAR units after surgery. Calculations are based on N = 897 patients. Preoperative duration, BCVA, and MLD were significant predictors of a postoperative BCVA of 0.3 logMAR or better.
BCVA = best-corrected visual acuity; CI = confidence interval; ICG = indocyanine green; iFTMH = idiopathic full-thickness macular hole; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MLD = minimum linear diameter; VA = visual acuity.
*Statistically significant results ($P \leq 0.05$).

interventions that surgeons can perform to improve outcomes. Consistent with current published literature, our findings confirm that ILM peeling improves closure rates and has no detrimental effect on vision in those achieving primary hole closure after surgery.[44] We also found that ILM flaps improve closure rates and, similar to ILM peeling, did not have a detrimental effect on VA in those with primary closure, consistent with findings of a recent published meta-analyses.[51]

There has been debate about the potential postoperative benefits that can be gained by face-down positioning after iFTMH surgery. The current evidence base suggests that the effects are likely to be small. In a randomized superiority RCT of iFTMH greater than 400 μm performed by Pasu et al,[41] hole closure rates of 95.5% were achieved for participants who were advised to perform face-down positioning after surgery compared with 85.6% who were not (OR, 3.15, $P = 0.08$). Although not statistically significant, this difference may be considered clinically relevant and would have important implications on the cost-effectiveness of the treatment. Although this was not a primary outcome, these authors also found the mean improvement in VA was 0.23 logMAR units higher in the face-down positioning group ($P = 0.01$). Likewise, we found an OR of 2.89 ($P = 0.021$) for closure with face-down positioning and a small beneficial effect for VA improvement in the total cohort (OR, −0.09, $P = 0.01$), although the latter was no longer the case when the analysis was restricted to those with primary closure. Pasu et al[41] found that the number of people needed to keep the face-down positioning to gain 1 extra closure is approximately 24 with a median hole size of 488 μm, similar to the median of 492 μm in our current study.

In our study, we also showed that using long-acting gas was associated with improved postoperative BCVA (coefficient 0.997, $P = 0.021$) and a trend toward BCVA improvement (−0.089, $P = 0.072$) in those with primary hole closure, but not for closure itself. This was unexpected because previous studies have not found this effect on BCVA.[25] Although Kelly and Wendel[52] used sulfur hexafluoride gas as a tamponade agent, when the procedure was subsequently adopted, most surgeons initially chose to use perfluoropropane (C3F8) gas to maintain gas-related hole bridging for as long as possible in an attempt to improve closure rates. However, there has been a gradual change in practice to increasing use of

Quality in Prognosis Studies (QUIPS) scores												
Risk of potential bias domains	Yorston et al, 2012	Yao et al, 2018	Pasu et al, 2020	Velez Montoya et al, 2018	Lange et al, 2012	Kwok et al, 2005	Michalewska et al, 2010	Lois et al, 2011	Christensen et al, 2008	Briand et al, 2015	Alberti et al, 2016	Manasi et al, 2018
Study Participation	Mod	Low	Low	Low	Low	Low	Mod	Low	Low	Low	Low	Low
Study Attrition	Low	Low	Low	Low	Low	Mod	Mod	Mod	Low	Mod	Mod	Mod
Study Measurements	Low	Low	Low	Mod	Low	Mod	Mod	Low	Low	Mod	Mod	Low
Outcome Measurements	Low	Low	Low	Mod	Low	Low	Low	Low	Low	Low	Low	Low
Study Confounding	Mod	Low	Low	Mod	Low	Mod	Mod	Mod	Mod	Low	Low	Mod
Statistical Analysis	Low	Low	Low	low	Low	Low	Mod	Low	Low	Low	Low	Low
Overall	**Low**	**Low**	**Low**	**Mod**	**Low**	**Mod**	**Mod**	**Low**	**Low**	**Low**	**Low**	**Low**
Overall GRADE certainty of evidence	**Mod**											

Figure 6. Nine of 12 included studies are considered at low risk of bias. The overall Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) certainty of evidence for the 12 studies is moderate. The outcome measures used to form this evaluation are the association between symptom duration (months) and postoperative macular hole closure (N = 915; odds ratio [OR], 0.965; 95% confidence interval [CI], 0.935–0.996; $P = 0.026$) and the association between symptom duration (months) and postoperative BCVA in logMAR units (N = 731; correlation coefficient: 0.008; 95% CI, 0.005–0.011; $P < 0.001$). mod = moderate; QUIPS = Quality in Prognosis Studies.

medium (C2F6) and short-acting gases (sulfur hexafluoride) or even air.[4,53] A recent systematic review did not find any clear beneficial effect of the gaseous tamponade used on closure rates or on BCVA, although the evidence base for these questions is weak.[54] Our findings regarding the benefits of long-acting tamponade should be interpreted with caution and reinforce the need for further well-designed studies on tamponade choice.

Study Limitations

Our study has several limitations. It is important to note that the randomized trials we included, and for which we performed the systematic review, were not assessing our primary end point, that is, the effect of symptom duration on macular hole outcomes. The trials included only symptom duration as an observed variable and did not analyze it. The trials were being performed for a variety of other end points as listed in Table 1. Furthermore, although all RCTs included recorded symptom duration, there was no common protocol for its definition. One study only recorded time from diagnosis to surgery, but a sensitivity analysis showed this had no effect on the findings.[25] Five of the included studies also only included 3-month follow-up data. We included "study" as a level in our modeling to account for heterogeneity between studies and the time period covered by the RCTs included. The median iFTMH size in our study was large compared with many patients who present in routine clinical practice, and although the geographical spread of countries included was large, there were none from the United States. It is likely that referral patterns and symptom durations at the time of surgery will vary from country to country, which limits the generalizability of our findings. The effect of symptom duration is also likely greater in smaller holes, and our analysis could have underestimated the magnitude of the effect.[4,55] Lens management differed between studies and could have confounded our results, but preoperative and postoperative lens status was included as a variable. Furthermore, we were unable to obtain IPD from all RCTs identified from our systematic literature search. This was determined solely by whether the corresponding authors were responsive and able to share their data with us for the analysis. However, comparison between the included and excluded study characteristics shows broad similarities.

Conclusions

This IPD meta-analysis found that symptom duration was independently associated with both anatomic and visual outcomes for people undergoing surgery for primary iFTMH. Early identification of those affected by this condition and early intervention that could be achieved by increasing public awareness and improving care pathways would improve treatment outcomes and should be prioritized by health services. The study had several limitations, and the quality of evidence was graded as "moderate." Future clinical studies should mandate standardized collection of symptom data allowing validation of our findings with, for example, defined randomization stratification for symptom duration or prospectively defined subgroup analyses.

Footnotes and Disclosures

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[1] Bioscience Institute, Newcastle University, Newcastle Upon Tyne, United Kingdom.

[2] Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom.

[3] Medical Statistics Team, University of Aberdeen, Aberdeen, United Kingdom.

[4] Sunderland Eye Infirmary, Queen Alexandra Road, Sunderland, United Kingdom.

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No animal subjects were used in this study.

Author Contributions:

Conception and design: Lois, Scott, Steel

Data collection: Murphy, Al-Zubaidy, Lois, Scott, Steel

Analysis and interpretation: Murphy, Al-Zubaidy, Lois, Scott, Steel

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Overall responsibility: Murphy, Al-Zubaidy, Lois, Scott, Steel

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CI** = confidence interval; **iFTMH** = idiopathic full-thickness macular hole; **ILM** = internal limiting membrane; **IPD** = individual participant data; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **MLD** = minimum linear diameter; **OR** = odds ratio; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **QUIPS** = Quality in Prognosis Studies; **RCT** = randomized controlled trial; **VA** = visual acuity.

Keywords:
Closure, Individual participant analysis, Macular hole, Randomized controlled trial, Symptom duration, Visual acuity.

Correspondence:
David H. Steel, MBBS, MD, Sunderland Eye Infirmary, Queen Alexandra Road, Sunderland, UK. E-mail: David.steel@ncl.ac.uk.

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