Title: The effect of macular hole duration on surgical outcomes: An individual participant data study of randomised controlled trials

Short title: The effect of macular hole duration on surgical outcomes

Authors

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]

Institutions

1. Bioscience Institute, Newcastle University, Newcastle Upon Tyne, UK
2. Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
3. School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK
4. Sunderland Eye Infirmary, Queen Alexandra Road, Sunderland, UK

Correspondence to:

Professor DH Steel
Sunderland Eye Infirmary, Queen Alexandra Road, Sunderland, UK
Email: David.steel@ncl.ac.uk
Telephone +44 (191) 5699065
Fax: +44 (191) 5699060

Macular hole duration study group

Contributors:

Name	Degrees	Study country	Affiliation (s) (institute, address, country)	Email address
Jinfeng Qu	MD	China	Department of Ophthalmology Peking University People's Hospital Beijing Key Laboratory for the Diagnosis and Treatment of Retinal and Choroid Diseases Xi Zhi Men South Ave #11 , Xi Cheng District Beijing, P.R. China, 100044	drbari@163.com
Mingwei Zhao	MD	China	Department of Ophthalmology Peking University People's Hospital Beijing Key Laboratory for the Diagnosis and Treatment of Retinal and Choroid Diseases Xi Zhi Men South Ave #11 , Xi Cheng District Beijing, P.R. China, 100044	dr_mingweizhao@163.com

Srinivas Sadda	MD	China	Doheny Eye Institute, UCLA, 150 N. Orange Grove Blvd, Pasadena, CA, 91103, USA	vassadda@gmail.com
Sreekumar Manasa	MD	India	SUT Academy of Medical Sciences, Thiruvananthapuram, Kerala, India	sendtomanasa@gmail.com
Divya Agarwal	MD, FICO	India	Vikalp Eye and Retina Centre, Bareilly, India	divyagrm@gmail.com
Atul Kumar	MD, FRCS (Ed)	India	AK Institute of Ophthalmology, New Delhi, India	atul56kumar@yahoo.com
Prateek Kakkar	MD, FICO	India	Reticure Eye Centre, Delhi, India	prateekkak@gmail.com
Serge Bourgault	MD, FRCSC	Canada	Département d'ophtalmologie et d'oto-rhino-laryngologie – chirurgie cervico-faciale, Centre Universitaire d'Ophtalmologie, Hôpital du Saint-Sacrement, CHU de Québec - Université Laval, Québec, QC, Canada	serge.bourgault.1@ulaval.ca
Eric Tourville	MD	Canada	Centre hospitalier universitaire université Laval, Quebec City	tourvillesoucy@hotmail.com
Raul Velez-Montoya	MD	Mexico	Retina Department, Asociación para Evitar la Ceguera en Mexico, Hospital "Dr. Luis Sanchez Bulnes" IAP, Vicente García Torres #46, Col: San Lucas Coyoacán, 04030 Mexico City, DF Mexico.	rvelezmx@yahoo.com
Sergio E. Hernandez-Da Mota	MD	Mexico	Ophthalmology Unit, Clinica David, Morelia City, Mexico.	tolodamota@yahoo.com.mx
J Abel Ramirez-Estudillo	MD	Mexico	Retina and Vitreous Department, Fundación Hospital Nuestra Señora de la Luz, Mexico City, Mexico.	ramirezestudillo@gmail.com
Jerzy Nawrocki	MD, PhD	Poland	Ophthalmic Clinic "Jasne Blonia", Rojna 90, 91- 134 Lodz, Poland	jerzy.nawrocki@poczt.onet.pl
Zofia Anna Nawrocka	MD, PhD	Poland	Ophthalmic Clinic "Jasne Blonia", Rojna 90, 91- 134 Lodz, Poland	zosia_n@yahoo.com
Clemens Lange	MD, PhD	UK (London Pilot)	University Eye Hospital Freiburg, Freiburg, Germany	clemens.lange@uniklinik-freiburg.de
James Bainbridge	MA, PhD	UK (PIMS)	Moorfields Eye Hospital, London, UK	j.bainbridge@ucl.ac.uk
Noemi Lois	PhD	United Kingdom (FILMS)	Wellcome Wolfson Institute For Experimental Medicine, Queen's University Belfast, Belfast, UK	n.lois@qub.ac.uk
David Yorston	MBChB	United Kingdom (Glasgow Pilot)	Tennent Institute of Ophthalmology, Gartnavel Hospital, Glasgow, Scotland, UK	dbyorston@btinternet.com

Mark Alberti	MD, PhD	Denmark	Faculty of health sciences, Rigshospitalet University of Copenhagen Denmark	mark.jensen.alberti@regionh.dk
Morten de la Cour	MD, PhD	Denmark	Faculty of health sciences, Rigshospitalet University of Copenhagen Denmark	morten.dornonville.de.la.cour@regionh.dk
Ulrik Christensen	MD, PhD	Denmark	Dept. of Ophthalmology, Rigshospitalet – Glostrup, Denmark	ulrik.correll.christensen@regionh.dk
Kwok Kwan Ho Alvin	MD, FRCS	Hong Kong	Department of Ophthalmology, The Hong Kong Sanatorium and Hospital, 2 Village Road, Happy Valley, Hong Kong, People's Republic of China.	alvinkwok@hksh.com

Precis: Symptom duration is independently associated with anatomical and vision outcomes for individuals undergoing surgery for Idiopathic full-thickness macular holes. The time to surgery should be minimised and care pathways designed to enable this.

Abstract (343/350 words)

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

Clinical relevance: iFTMH 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 unclear.

Methods: A systematic review identified eligible RCTs which included adults with iFTMH undergoing vitrectomy with gas tamponade where symptom duration, primary iFTMH closure and post-operative BCVA were recorded. Bibliographic databases were searched for articles published between 2000 and 2020. IPD was requested from eligible studies.

***Results*:** 20 eligible RCTs were identified. Data was requested from all studies and obtained from 12 representing 940 eyes in total. Median symptom duration was 6-months (interquartile (IQR) range 3-10).

Primary closure was achieved in 81.5% of eyes. The 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% CI: 0.935 to 0.996, p=0.026). Internal limiting membrane (ILM) peeling, intra-operative ILM flap use, better pre-operative BCVA, face-down positioning and smaller iFTMH size were associated with increased odds of primary closure.

Mean post-operative BCVA in eyes achieving primary closure was 0.52 logMAR (20/66). 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 to 0.011, p<0.001) (i.e., approximately 1 ETDRS letter loss per two months). ILM flaps, intra-ocular tamponade using long-acting gas, better pre-operative BCVA, smaller iFTMH size and phakic status were also associated with improved post-operative BCVA.

***Conclusions*:**

Symptom duration was independently associated with both anatomical and visual outcomes in persons undergoing surgery for iFTMH. Time to surgery for iFTMHs should be minimised and care pathways designed to enable this.

Key words: Macular hole, randomised controlled trial, symptom duration, closure, visual acuity, individual participant analysis

Introduction

An Idiopathic full thickness macular hole (iFTMH) is a common and visually disabling retinal disorder. They occur bilaterally in 10% of cases. Incidence is approximately 4-8 per 100,000 per annum, and it increases to 200 per 100,000 in females aged between 60 to 70 years[1,2]. If left untreated they 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 two main outcomes which indicate surgical success following surgery to treat IFTMHs: iFTMH hole closure and final post-operative vision. For iFTMHs with a minimum linear diameter (MLD) measurement less than 500μm, primary hole closure occurs in 85-95% of cases; as the size of the hole increases, the rates of hole closure reduce[4]. The visual acuity achieved after surgery with successful hole closure is variable; roughly 60% gain at least 0.3 logarithm of the minimum angle of resolution (logMAR) units, but only 35-40% achieve vision sufficient to legally allow them to drive a motorised vehicle in the United Kingdom (20/40)[5].

Several factors have been proposed to affect both post-operative hole closure and vision, most notably iFTMH size. Pre-operative BCVA is also known to be highly correlated with post-operative vision after successful hole closure[6]. The length of time a hole has been present for before surgery, typically estimated by the symptom duration, termed the 'duration' hereon, is also thought to affect both post-operative hole closure and vision.

To date, there have been no prospective studies specifically designed to investigate the effects of symptom duration on iFTMH outcomes following surgery. Published literature shows that the current evidence of the link between duration and iFTMH closure and post-operative vision is variable. Some studies, including three which used large databases, suggest an association between duration and post-operative hole closure and BCVA[7–11]. At least five other studies investigating different treatments for iFTMHs, including one randomised controlled trial (RCT), found no effect [12–16]. However, these studies have several important limitations, which include inaccurate recordings of visual acuity for example using recordings which 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 pre-operative VA; with time the hole enlarges and vision deteriorates. This association both enhances the effect of duration and confounds studies which aim to analyse the effect of duration on outcomes. Understanding exactly how duration affects anatomical and functional outcomes following 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 following iFTMH surgery using individual participant data (IPD) obtained from previously published RCTs presenting surgical outcomes of FTMHs which included data on symptom duration. We obtained individual participant data from RCTs for the purpose of the analysis presented herein as 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. 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 of systematic reviews of interventions[17] and the PRISMA statement[18].

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 Organisation International clinical trials registry platform). (See **supplementary material 1**) Reference lists of eligible studies and previously published review articles were also searched to identify other potentially eligible studies which 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 randomised controlled trials (RCT) which included adult (≥18 years) participants with an iFTMH who underwent vitrectomy surgery with gas or air tamponade in association with any of the following manoeuvres: internal limiting membrane (ILM) peeling of any size or type, ILM flap, cataract surgery, any type of staining for ILM (and/or associated epiretinal membrane (ERM)), and any type of post-operative positioning protocol. We only included RCTs where 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 which investigated secondary macular holes, including those which developed in association with trauma, retinal detachment, myopia >6 dioptres or retinal dystrophies. Similarly, 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 (AMD) and diabetic macular oedema). We excluded all studies which were not RCTs.

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

For those considered eligible for inclusion, we requested IPD from the corresponding authors by email. We allowed the corresponding author two months to reply to our email correspondence in total. If no reply was received after four 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 one eye per patient was included in the IPD, and in studies which included participants who had undergone iFTMH surgery to both eyes, we included data corresponding to the eye which first underwent surgery only.

As 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 which has been used in other IPD analyses of studies investigating prognostic indicators[19–21]. For the assessment six 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 three up to seven 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 two 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 six domains, with at least four rated as low (of which the outcome measurement domain must be rated as low at least). A study was scored as high risk of bias if two 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 two surgical outcome: primary anatomical closure of the iFTMH (i.e., surgical closure following first surgery) and BCVA at 6-months post-operatively. If post-operative BCVA data was not available at 6-months, we used the nearest available time. The difference between pre-operative BCVA to post-operative BCVA was included as a secondary endpoint. All visual acuity 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 (GRADE) 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 versus 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)

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 intra-operative adjuvants (yes/no), the use of indocyanine green staining (yes/no), the type of gaseous tamponade used, pre-operative BCVA, post-operative 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 visual acuity analysis) (reference category); 2) phakic pre-operatively and post-operatively at the-time point used for BCVA measurement; and 3) phakic pre-operatively and pseudophakic at the time-point chosen for measuring BCVA. We expressed results using odds ratios (OR) and their 95% confidence intervals (CI). The model was then used to estimate predicted probabilities of hole closure with 95% CIs for combinations of iFTMH duration, iFTMH size, and pre-operative BCVA.

A similar multilevel regression model was examined the effect of duration on post-operative BCVA for those with primary iFTMH closure whilst adjusting for the same covariates as above.

Additional analyses were conducted to investigate the effect of duration on post-operative BCVA for all patients, and the effect of duration on change in BCVA from baseline for all patients and for those

who achieved successful post-operative iFTMH closure. Another analysis investigated the effect of duration on achieving a post-operative BCVA of logMAR≥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 to 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 non-linear effect on the primary outcomes.

The relationship between duration and iFTMH post-operative hole closure and the relationship between hole size and closure were tabulated.

Results

We identified 20 eligible RCTs[15,25,34–43,26–33]. We attempted to contact all corresponding authors via email and requires individual participant data (IPD) from their study participants. In total, 12 studies provided IPD which represented 940 eyes[25,28,43,44,33–37,40–42].

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

Population and study characteristics

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

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

The median MLD was 492µm (400-624) and pre-operative 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 where we could not obtain IPD and which were therefore not included are shown in **supplementary material 2 and 3**.

Relationship between hole size, baseline visual acuity 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 anatomical closure

Post-operative iFTMH closure following the first surgical intervention (termed primary closure) was achieved in 761/934 (81.5%) eyes. 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) (**figure 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 symptom duration was linear (**figure 4**).

To illustrate the effects of duration on hole closure, we have developed a table containing predicted probabilities for iFTMH primary closure which compare five iFTMH sizes (MLD measurements

200µm, 300µm, 450µm, 600µm and 800µm) with three specific pre-operative 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 4).**

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 to 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 pre-operative BCVA, post-operative face-down positioning and a smaller size hole (MLD). When predicting iFTMH closure, one additional month of symptom duration was approximately equivalent in effect to an additional 10µm of MLD size.

Post-operative vision outcomes

The median post-operative BCVA at six-months follow-up was 0.5 logMAR (Snellen equivalent: 20/63) (IQR: 0.3-0.78) (N=914). The median post-operative BCVA for eyes following primary hole closure (n=747) was 0.48 logMAR (Snellen equivalent: 20/60) (IQR: 0.3-0.7).

The relationship between symptom duration and post-operative visual outcomes is shown in **figure 5**.

The outputs from a multilevel linear regression model predicting post-operative BCVA for eyes with successful primary IFTMH closure based on relevant pre-operative 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 to 0.011, p<0.001) for post-operative BCVA at six-months (i.e., visual acuity deteriorates). This means that for every 10 months of extra duration, independent of hole size increase or pre-operative visual acuity reduction during that time, there was a drop of approximately 1 line of Snellen acuity in post-operative BCVA e.g., 20/40 to 20/32) The intra-operative use of ILM flaps, long-acting gas tamponade, better pre-operative BCVA, smaller hole size (MLD) and phakic status were associated with improved post-operative BCVA. When considering BCVA at six-months follow-up, each additional month of symptom duration is approximately equivalent to 40µm of iFTMH size (MLD).

Models with interaction terms

For the two primary outcomes, three additional interaction terms for each pairwise combination of duration, hole size and pre-operative visual acuity were added to the model to investigate whether any combination of these variables had a non-linear effect on the probability of hole closure or post-operative 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 post-operative visual acuity is linear.

Sensitivity analysis with exclusion of Briand et al.

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 analysed the data after excluding the Briand et al study. The results were very similar. An additional month of duration of the iFTMH was associated with odds of primary closure of 0.964 (95% CI: 0.934 to 0.996) (p=0.026, n=857) and increased post-operative logMAR of 0.008 (95% CI: 0.005 to 0.011) (p<0.001, n=685).

Secondary analyses

Symptom duration had a similar effect on post-operative BCVA when the analysis included both patients who achieved iFTMH closure and those who did not **(Supplementary material 5)**.

When examining the change in visual acuity 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 post-operative BCVA of 0.3 or better (odds ratio: 0.065, p=0.006), as were pre-operative visual acuity (odds ratio: 2.848, p=<0.001) and MLD (odds ratio: 0.003, p=0.001) **(Table 8)**.

Study quality and risk of bias

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

Overall certainty of evidence:

Using a modified GRADE approach, as detailed in our methods, we graded the overall certainly of evidence for the included studies as 'Moderate'. (**Figure 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 anatomical (i.e., lower rates of hole closure) and visual outcomes (i.e., less BCVA improvement following surgery and lower final post-operative vision) following surgery. The effect was independent of pre-operative hole size and visual acuity. 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 anatomical and visual outcomes. As a result, we confirmed that ILM peeling improves hole closure, as does the use of ILM flaps intra-operatively and post-operative face-down positioning. In addition, we showed that post-operative vision is improved following the use of ILM flaps and long-acting gas for tamponade.

Patients with iFTMHs can present with varying signs and symptoms. Their symptom duration, extent of visual acuity loss and the size of their hole can be highly variable. In our study we found all three characteristics were interrelated (i.e., a longer duration was associated with a larger hole size and worse visual acuity at presentation), however each were also independently associated with anatomical and visual outcomes. The size of the iFTMH at presentation was very 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 hence presenting late especially if it is their non-dominant eye effected for example. It may also relate to anatomical 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 growing faster than larger holes [47,48] . The effect of hole size and duration on post-operative outcomes were 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 200µm iFTMH and 0.48 logMAR pre-operative BCVA with a 6-month history of symptoms that increases to 400µm 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 a near 300% relative increased risk of non-closure. 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 following surgery. Based on 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 three components. Firstly, there is the symptom duration at first presentation to any care provider; secondly 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 finally, any waiting time from diagnosis to surgery. All three will vary widely by population and health care system. A United Kingdom (UK) database study found that the median total duration of macular holes was 4 months at presentation, with 7% being greater than 12 months. During the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, in the UK iFTMH surgery was not prioritised and anecdotally waiting times have significantly increased[50]. This study has shown the importance of duration of the iFTMH on postoperative anatomical and visual outcomes and supports the development of prioritisation 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 health care 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 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 following surgery[44]. We also found that ILM flaps improve closure rates and, similarly to ILM peeling, did not have a detrimental effect on visual acuity in those with primary closure, consistent with findings of a recent published meta-analyses [51].

There has been debate about the potential post-operative benefits which 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 randomised superiority RCT of iFTMH greater than 400 microns 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 (Odds ratio (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. Interestingly, although 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). Similarly, we found an ORs 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 found that the number of people needed to keep the face down positioning to gain one extra closure is approximately 24 with a median hole size of 488 microns, similar to the median of 492µm in our current study.

In our study, we also showed that using long-acting gas was associated with improved post-operative BCVA (coefficient 0.997, p=0.021), and a trend towards BCVA improvement (-0.089, p=0.072) in those with primary hole closure, but not for closure itself. This was unexpected as previous studies have not found this effect on BCVA[25]. Although Kelly and Wendel[52] used Sulfur hexafluoride (SF6) 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 medium (C2F6) and short-acting gases (SF6) or even air[4,53]. A recent systematic review did not find any clear beneficial effect of the gaseous tamponade used on closure rates, nor 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 into tamponade choice.

Our study has several limitations. It is important to note that the randomised trials we included, and for which we performed the systematic review, were not assessing our primary endpoint, i.e., the effect of symptom duration on macular hole outcomes. The trials included only symptom duration as an observed variable and didn't analyse it. The trials were being performed for a variety of other endpoints as listed in table 1. Furthermore, whilst 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 modelling 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 the although the geographical spread of countries included was large there were none from the USA for example. It is likely that referral patterns and symptom durations at the time of surgery will vary from country to country, which limit the generalisability of our findings. The effect of symptom duration is also likely greater in smaller holes and our analysis could have under-estimated the magnitude of the effect[4,55]. Lens management differed between studies and could have confounded our results but pre-operative and post-operative 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. Comparison however between the included and excluded study characteristics shows broad similarities.

In conclusion, this IPD meta-analysis found that symptom duration was independently associated with both anatomical and visual outcomes for people undergoing surgery for primary iFTMH. Early identification of those affected by this condition, and early intervention which could be achieved by increasing public awareness and improving care pathways, would improve treatment outcomes and should be prioritised 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.

Funding: None

References

1. Ali FS, Stein JD, Blachley TS, Ackley S, Stewart JM. Incidence of and Risk Factors for Developing Idiopathic Macular Hole Among a Diverse Group of Patients Throughout the United States. JAMA Ophthalmol. 2017;135(4):299-305.

2. McCannel CA, Ensminger JL, Diehl NN, Hodge DN. Population-based incidence of macular holes. Ophthalmology. 2009;116(7):1366-1369.

3. McKibbin M, Farragher TM, Shickle D. Monocular and binocular visual impairment in the UK Biobank study: prevalence, associations and diagnoses. BMJ open Ophthalmol. 2018;3(1).

4. Steel DH, Donachie PHJ, Aylward GW, et al. Factors affecting anatomical and visual outcome after macular hole surgery: findings from a large prospective UK cohort. Eye (Lond). 2021;35(1):316-325.

5. Jackson TL, Donachie PHJ, Sparrow JM, Johnston RL. United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery: Report 2, Macular Hole. Ophthalmology. 2013;120(3):629-634.

6. Murphy DC, Nasrulloh A V., Lendrem C, et al. Predicting Postoperative Vision for Macular Hole with Automated Image Analysis. Ophthalmol Retin. 2020;4(12):1211-1213.

7. Essex RW, Hunyor AP, Moreno-Betancur M, et al. The Visual Outcomes of Macular Hole Surgery: A Registry-Based Study by the Australian and New Zealand Society of Retinal Specialists. Ophthalmol Retin. 2018;2(11):1143-1151.

8. Jaycock PD, Bunce C, Xing W, et al. Outcomes of macular hole surgery: implications for surgical management and clinical governance. Eye. 2005;19(8):879-884.

9. Kang HK, Chang AA, Beaumont PE. The macular hole: report of an Australian surgical series and meta-analysis of the literature. Clin Experiment Ophthalmol. 2000;28(4):298-308.

10. Tognetto D, Grandin R, Sanguinetti G, et al. Internal limiting membrane removal during macular hole surgery: results of a multicenter retrospective study. Ophthalmology. 2006;113(8):1401-1410.

11. Ullrich S, Haritoglou C, Gass C, Schaumberger M, Ulbig MW, Kampik A. Macular hole size as a prognostic factor in macular hole surgery. Br J Ophthalmol. 2002;86(4):390-393.

12. Kumagai K, Ogino N, Demizu S, et al. Variables That Influence Visual Acuity After Macular Hole Surgery. Jpn J Ophthalmol. 2001;45(1):112.

13. Stene-Johansen I, Bragadóttir R, Petrovski BÉ, Petrovski G. Macular Hole Surgery Using Gas Tamponade-An Outcome from the Oslo Retrospective Cross-Sectional Study. J Clin Med. 2019;8(5).

14. Gupta B, Laidlaw DAH, Williamson TH, Shah SP, Wong R, Wren S. Predicting visual success in macular hole surgery. Br J Ophthalmol. 2009;93(11):1488-1491.

15. Ezra E, Gregor ZJ. Surgery for idiopathic full-thickness macular hole: two-year results of a randomized clinical trial comparing natural history, vitrectomy, and vitrectomy plus autologous serum: Morfields Macular Hole Study Group RAeport no. 1. Arch Ophthalmol (Chicago, Ill 1960). 2004;122(2):224-236.

16. Alberti M, Hermann MN, Christensen UC, Cour M la. Progression of full-thickness macular holes prior to surgery. Invest Ophthalmol Vis Sci. 2019;60(9):2016-2016.

17. Higgins J, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane. 2020.

18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med. 2009;6(7):e1000100.

19. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-286.

20. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144(6):427-437.

21. The Cochrane Collaboration. QUIPS Tool. Cochrane. 2022.

22. Den Bakker CM, Anema JR, Zaman ACGNM, et al. Prognostic factors for return to work and work disability among colorectal cancer survivors; A systematic review. PLoS One. 2018;13(8):e0200720-e0200720.

23. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013;120(12):2611-2619.

24. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015;350.

25. Briand S, Chalifoux E, Tourville E, et al. Prospective randomized trial: outcomes of SF_6 versus C_3F_8 in macular hole surgery. Can J Ophthalmol. 2015;50(2):95-100.

26. Casini G, Mura M, Figus M, et al. INVERTED INTERNAL LIMITING MEMBRANE FLAP TECHNIQUE FOR MACULAR HOLE SURGERY WITHOUT EXTRA MANIPULATION OF THE FLAP. Retina. 2017;37(11):2138-2144.

27. Cho HY, Kim YT, Kang SW. Laser Photocoagulation as Adjuvant Therapy to Surgery for Large Macular Holes. Korean J Ophthalmol. 2006;20(2):93.

28. Christensen UC, Krøyer K, Sander B, et al. Value of internal limiting membrane peeling in surgery for idiopathic macular hole stage 2 and 3: a randomised clinical trial. Br J Ophthalmol. 2009;93(8):1005-1015.

29. Cillino S, Castellucci M, Cillino G, et al. Infracyanine Green vs. Brilliant Blue G in Inverted Flap Surgery for Large Macular Holes: A Long-Term Swept-Source OCT Analysis. Medicina (Kaunas). 2020;56(1).

30. Ghosh B, Arora S, Goel N, et al. Comparative evaluation of sequential intraoperative use of whole blood followed by brilliant blue versus conventional brilliant blue staining of internal limiting membrane in macular hole surgery. Retina. 2016;36(8):1463-1468.

31. Hu BJ, Du XL, Li WB, et al. Incomplete fluid-air exchange technique for idiopathic macular hole surgery. Int J Ophthalmol. 2019;12(10):1582.

32. Lauritzen DB, Hampton GR, Torrisi PF, Rutledge BK, Delaney W V., Spalding SC. Macular hole surgery: A randomized controlled trial using autologous serum adjuvant. Ann Ophthalmol 2003 352. 2003;35(2):123-129.

33. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted Internal Limiting Membrane Flap Technique for Large Macular Holes. Ophthalmology. 2010;117(10):2018-2025.

34. Manasa S, Kakkar P, Kumar A, Chandra P, Kumar V, Ravani R. Comparative Evaluation of Standard ILM Peel With Inverted ILM Flap Technique In Large Macular Holes: A Prospective, Randomized Study. Ophthalmic Surg Lasers Imaging Retina. 2018;49(4):236-240.

35. Lois N, Burr J, Norrie J, et al. Internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole: a pragmatic randomized controlled trial. Invest Ophthalmol Vis Sci. 2011;52(3):1586-1592.

36. Velez-Montoya R, Ramirez-Estudillo JA, de Liano CSG, et al. Inverted ILM flap, free ILM flap and conventional ILM peeling for large macular holes. Int J Retin Vitr. 2018;4(1):8.

37. Yao Y, Qu J, Dong C, et al. The impact of extent of internal limiting membrane peeling on anatomical outcomes of macular hole surgery: results of a 54-week randomized clinical trial. Acta Ophthalmol. 2019;97(3):303-312.

38. Kwok AK, Lai TY, Wong VW. Idiopathic macular hole surgery in Chinese patients: a randomised study to compare indocyanine green-assisted internal limiting membrane peeling with no internal limiting membrane peeling. Hong Kong Med J. 2005 Aug;11(4):259-66

39. Zhang Y, Zhang Y, Chen X, et al. Facedown positioning after vitrectomy will not facilitate macular hole closure based on swept-source optical coherence tomography imaging in gas-filled eyes: A Prospective, Randomized Comparative Interventional Study. Retina. 2019;39(12):2353-2359.

40. Yorston D, Siddiqui MAR, Awan MA, Walker S, Bunce C, Bainbridge JW. Pilot randomised controlled trial of face-down posturing following phacovitrectomy for macular hole. Eye. 2012;26(2):267.

41. Pasu S, Bell L, Zenasni Z, et al. Facedown Positioning Following Surgery for Large Full-Thickness Macular Hole: A Multicenter Randomized Clinical Trial. JAMA Ophthalmol. 2020;138(7):725-730.

42. Alberti M, La Cour M. NONSUPINE POSITIONING IN MACULAR HOLE SURGERY: A Noninferiority Randomized Clinical Trial. Retina. 2016;36(11):2072-2079.

43. Lange CAK, Membrey L, Ahmad N, et al. Pilot randomised controlled trial of face-down positioning following macular hole surgery. Eye (Lond). 2012;26(2):272-277.

44. Spiteri Cornish K, Lois N, Scott NW, et al. Vitrectomy with internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole. Ophthalmology. 2014;121(3):649-655.

45. Grinton M, Melville H, George G, et al. Determinants of vitreomacular traction width: associations with foveal floor width and vitreoretinal interface changes. Acta Ophthalmol. 2021;99(5):e700-e705.

46. Murphy DC, Melville HJR, George G, et al. The Association between Foveal Floor Measurements and Macular Hole Size. Ophthalmol Retin. 2021;5(7):680-686.

47. Madi HA, Dinah C, Rees J, Steel DHW. The Case Mix of Patients Presenting with Full-Thickness Macular Holes and Progression before Surgery: Implications for Optimum Management. Ophthalmologica. 2015;233(3-4):216-221.

48. Berton M, Robins J, Frigo AC, Wong R. Rate of progression of idiopathic full-thickness macular holes before surgery. Eye (Lond). 2020;34(8):1386-1391.

49. Uwaydat SH, Mansour A, Ascaso FJ, et al. Clinical characteristics of full thickness macular holes that closed without surgery. Br J Ophthalmol. 2021; bjophthalmol-2021-319001.

50. The Royal College of Ophthalmologists. Guidance document: Prioritisation of ophthalmic procedures. R Coll Ophthalmol. 2020.

51. Yu JG, Wang J, Xiang Y. Inverted Internal Limiting Membrane Flap Technique versus Internal Limiting Membrane Peeling for Large Macular Holes: A Meta-Analysis of Randomized Controlled Trials. Ophthalmic Res. 2021;64(5):713-722.

52. Kelly NE, Wendel RT. Vitreous Surgery for Idiopathic Macular Holes: Results of a Pilot Study. Arch Ophthalmol. 1991;109(5):654-659.

53. Essex RW, Kingston ZS, Moreno-Betancur M, et al. The Effect of Postoperative Face-Down Positioning and of Long- versus Short-Acting Gas in Macular Hole Surgery: Results of a Registry-Based Study. Ophthalmology. 2016;123(5):1129-1136.

54. Dervenis N, Dervenis P, Sandinha T, Murphy DC, Steel DH. Intraocular tamponade choice with vitrectomy and ILM peeling for idiopathic macular hole; a systematic review and meta-analysis. Ophthalmol Retin . 2022;0(0).

55. Essex RW, Hunyor AP, Moreno-Betancur M, et al. The Visual Outcomes of Macular Hole Surgery: A Registry-Based Study by the Australian and New Zealand Society of Retinal Specialists. Ophthalmol Retin. 2018;2(11):1143-1151.

Figure legends

Figure 1:

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

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.

Figure 3

Median duration of symptoms in those who achieved idiopathic full-thickness macular hole (iFTMH) closure following 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).

Abbreviations: IQR: interquartile range; iFTMH: idiopathic full-thickness macular hole; n; number

Figure 4

Dot plot of predicted probability of idiopathic full-thickness macular hole MH primary closure according to symptom duration. As duration increases, the predicted probability of primary closure reduces.

Figure 5

Scatter graph showing the association between symptom duration and best corrected visual acuity six-months following successful surgery. As symptom duration increases, post-operative vision worsens (increase in logMAR units).

Abbreviations: logMAR: Logarithm of the minimum angle of resolution