Analyse des facteurs cliniques et structurels associés à l'acuité visuelle post-opératoire des trous maculaires ayant subi une vitrectomie

Mémoire

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Sous la direction de :

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Résumé

Le trou maculaire (TM) est un défaut dans la rétine au niveau de la zone centrale de la macula (fovéa). Typiquement, les patients atteints de cette pathologie auront une diminution de leur acuité visuelle (AV) et de la métamorphopsie. Le traitement pour ces patients consistera en une vitrectomie par la pars plana (VPP) dans laquelle le vitré est retiré et remplacé par une tamponnade (SF_6, C_3F_8, air ou huile de silicone). Après cette chirurgie, le succès chirurgical, soit de fermeture anatomique du TM, est très élevé. Toutefois, plus récemment, on s'aperçoit que malgré un taux de fermeture anatomique élevé, les résultats visuels après l'intervention chirurgicale ne sont pas aussi importants, d'où la nécessité d'identifier les facteurs pronostiques liés à la VPP dans les TM qui ont fermé chirurgicalement et de tenter de prédire les résultats visuels suivant la VPP. En ce qui concerne les TM qui n'ont pas fermé lors d'une première VPP, il est intéressant d'évaluer les résultats fonctionnels et anatomiques à la suite d'une VPP de reprise. Nos travaux ont démontré que les yeux avec une durée du TM plus courte, une taille du TM plus petite et une AV préopératoire plus élevée ont obtenu de meilleurs résultats visuels après une première chirurgie réussie. Nous avons par la suite produit un modèle hybride basé sur des données cliniques et des tomographies par cohérence optique haute définition (HD-OCT) préopératoires de TM, et ce, à l'aide de l'intelligence artificielle, afin de tenter de mieux prédire les résultats visuels. Les modèles basés sur les données cliniques ou les HD-OCT ont obtenu de bonnes performances discriminantes individuellement. Toutefois, la combinaison des deux modèles dans un modèle hybride n'a pas significativement amélioré les performances. Enfin, les TM qui subissaient une VPP de révision (non-fermeture chirurgicale à la première VPP) montraient une fermeture anatomique dans 85% des cas et avaient une amélioration de l'AV au fil du temps.

Abstract

Idiopathic full thickness macular hole (MH) is a defect of all layers of the fovea. Typically, patients with this condition will experiment decreased visual acuity (VA) and metamorphopsia. Treatment for these patients will consist in a pars plana vitrectomy in which the vitreous is removed and replaced by a tamponade (SF_6, C_3F_8, air or silicone oil). After this surgery, the surgical success, or anatomical closure of the MH, is very high. However, more recently, it has been noticed that despite a high anatomical closure rate, the visual results after the surgery are not quite as important, hence the need to identify the prognostic factors related to vitrectomy in patients with closed MH and to predict visual results following vitrectomy. For MH that did not close during the primary vitrectomy, it is interesting to assess the functional and anatomical results following a revision vitrectomy. Our works provided that eyes with shorter MH duration, smaller MH size and higher preoperative VA achieved better visual outcomes after successful MH surgery. We then produced a hybrid model based on clinical data and preoperative MH high-definition optical coherence tomography (HD-OCT), using artificial intelligence to try to better predict visual results. Both the clinical data and HD-OCT models had good discriminative performances. Combining both into a hybrid model did not significantly improve performance. Finally, MH that underwent revision vitrectomy (nonsurgical closure at primary vitrectomy) showed anatomical closure in 85% of cases and had VA improvement over the time.

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Liste des abréviations

ACC : *Accuracy*
AP : Apprentissage profond
AMD : *Age-related macular degeneration*
ASC : Aire sous la courbe
AUC *: Area under the curve*
AUROC : *Area under the receiver operating characteristic curve*
AV : Acuité visuelle
BCVA : *Best-corrected visual acuity*
CI : *Confidence interval*
CNN : *Convolutional neural network*
CVA : *Corrected visual acuity*
DL *: Deep learning*
ELM : *External limiting membrane*
ETDRS : *Early Treatment Diabetic Retinopathy Study*
EZ : *Ellipsoid zone*
GCL : *Ganglion cell layer*
Grad-CAM : *Gradient-weighted Class Activation Mapping*
ICG : *Indocyanine green*
ILM : *Internal limiting membrane*
INL : *Inner nuclear layer*
IPL : *Inner plexiform layer*
logMAR : *Logarithm of the minimum angle of resolution*
MAVC : Meilleure acuité visuelle corrigée
MH : *Macular hole*
MHI : *Macular hole index*
NFL : *Nerve fiber layer*
NPV : *Negative predictive value*
OCT : *Optical coherence tomography*
ONL : *Outer nuclear layer*
OPL : *Outer plexiform layer*
OR : *Odds ratio*
PPV : *Positive predictive value*
PVD : *Posterior vitreous detachment*
RNC : Réseau neuronal convolutif
ROC : *Receiver operating characteristic*
RPE : *Retinal pigment epithelium*
SN : *Sensitivity*
SP : *Specificity*
TB : *Trypan blue*
TM : Trou maculaire
VA *: Visual acuity*
VPP : Vitrectomie par la pars plana

À mes parents, fidèles supporteurs qui m'ont toujours épaulé

Aux patients, qui sont le fondement et la motivation de cette recherche

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Également, je tiens à remercier Mathieu Godbout et Audrey Durand pour leur apport considérable tout au long de notre projet en lien avec l'intelligence artificielle.

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Finalement, je remercie mes ami(e)s et ma famille pour leurs encouragements et leur support constant face aux défis et embûches qu'apporte la réalisation d'une maîtrise dans le contexte des études en médecine en simultané (M.D.-M.Sc.).

Avant-propos

Le présent mémoire intitulé « Analyse des facteurs cliniques et structurels associés à l'acuité visuelle post-opératoire des trous maculaires ayant subi une vitrectomie » est présenté à la Faculté des études supérieures de l'Université Laval sous la forme d'insertion d'articles. Le premier article présenté au Chapitre 1 expose les facteurs pronostiques dans une visée fonctionnelle des trous maculaires ayant fermé chirurgicalement après une vitrectomie par la pars plana (VPP). Le deuxième article présenté au Chapitre 2 met de l'avant l'expertise acquise dans l'article précédent, ce qui culmine par le développement et la validation d'un algorithme d'intelligence artificielle basé sur des données cliniques et anatomiques (OCT) permettant la prédiction visuelle après la VPP. Enfin, le troisième article présenté au Chapitre 3 porte spécifiquement sur les trous maculaires qui ont échoué à une première VPP dans la trame d'une analyse anatomique et fonctionnelle.

L'article *Prognostic factors for visual outcomes in closed idiopathic macular holes after vitrectomy: outcomes at 4 years in a monocentric study* (Chapitre 1) a été accepté le 6 avril 2022 dans le *Journal of Ophthalmology*. Alexandre Lachance est le premier auteur. Dr Ali Dirani a conceptualisé le projet et a supervisé l'exécution du projet. Alexandre Lachance a examiné la proposition, recueilli les données, interprété les résultats et rédigé le manuscrit. Dre Mélanie Hébert a procédé à l'analyse statistique. Dre Mélanie Hébert, Dr Eunice You, Dr Jean-Philippe Rozon, Dr Serge Bourgault, Dr Mathieu Caissie et Dr Éric Tourville ont participé à la rédaction, à la révision et à l'édition de l'article. Tous les coauteurs ont revu le manuscrit et approuvé le manuscrit final. Également, les données préliminaires de cet article ont été présentées dans les congrès internationaux suivant : 127e congrès de la Société Française d'Ophtalmologie (mai 2021) et le Congrès annuel et exposition 2021 de la Société Canadienne d'Ophtalmologie (juin 2021).

Pour le deuxième article intitulé *Predicting visual improvement after macular hole surgery: a combined model using deep learning and clinical features* (Chapitre 3), il a été publié le 6 avril 2022 dans le journal *Translational Vision Science & Technology*. Alexandre Lachance est le premier auteur. Alexandre Lachance et Dr Ali Dirani ont conceptualisé le projet. Ce dernier a aussi supervisé l'exécution du projet avec l'aide de Audrey Durand. Alexandre Lachance a recueilli les données, interprété les résultats et rédigé le manuscrit. Mathieu Godbout, étudiant au Doctorat en informatique spécialisé en intelligence artificielle, a procédé à la conception informatique du développement du modèle. Dr Fares Antaki, Dre Mélanie Hébert, Dr Serge Bourgault, Dr Mathieu Caissie, Dr Éric Tourville et Audrey Durand ont participé à la rédaction, à la révision et à l'édition de l'article. Tous les coauteurs ont revu le manuscrit et approuvé le manuscrit final. Également, les résultats de cet article ont été présentés oralement dans les congrès de grande envergure suivant : Association for Research in Vision and Ophthalmology Annual Meeting (mai 2022) et la Journée Annuelle de la Recherche en Ophtalmologie de l'Université Laval (mai 2022).

Pour le troisième article nommé *Revision Surgery for Idiopathic Macular Hole after Failed Primary Vitrectomy* (Chapitre 2), il a été publié le 7 janvier 2021 dans le *Journal of Ophthalmology*. Alexandre Lachance est le premier auteur. Dr Ali Dirani a conceptualisé le projet et a supervisé l'exécution du projet. Alexandre Lachance a examiné la proposition, recueilli les données, procédé à l'analyse statistique, interprété les résultats et rédigé le manuscrit. Dr Eunice You, Dr Jérôme Garneau, Dr Serge Bourgault, Dr Mathieu Caissie et Dr Éric Tourville ont participé à la rédaction, à la révision et à l'édition de l'article. Tous les coauteurs ont revu le manuscrit et approuvé le manuscrit final. Également, les résultats de cet article ont été présentés dans les congrès suivant : Association for Research in Vision and Ophthalmology Annual Meeting (mai 2020), Journée Annuelle de la Recherche en Ophtalmologie de l'Université Laval (juin 2020) et Congrès annuel et exposition 2021 de la Société Canadienne d'Ophtalmologie (juin 2021).

Introduction

I.1 Anatomie du segment postérieur de l'œil

Le segment postérieur est associé aux composantes de l'œil situées postérieurement au cristallin. La chambre antérieure ne sera pas abordée dans ce mémoire puisqu'elle est moins pertinente en lien avec le sujet à l'étude.

I.1.1 La cavité vitréenne

La cavité vitréenne occupe la majorité du globe oculaire (volume de 4,4 cc; 2/3 du volume total de l'oeil) et elle est délimitée par la rétine en postérieur et en antérieur par les corps ciliaires et la partie postérieure du cristallin [1]. Au sein de cette cavité, on retrouve l'humeur vitrée (ou corps vitré) qui a une consistance plus gélatineuse en périphérie qu'au centre. L'humeur vitrée est entourée d'une fine couche de collagène la séparant des autres structures oculaires et avec lesquelles elle aura des adhérences. La membrane hyaloïde postérieure sépare le vitré de la rétine et la membrane hyaloïde antérieure quant à elle le sépare plutôt de la partie postérieure du cristallin. Les adhérences du vitré sont présentes en antérieur principalement à la pars plana et l'ora serrata. Les adhérences en postérieur sont beaucoup moins solides et elles sont principalement présentes au niveau des marges du disque optique, de la macula et des vaisseaux rétiniens.

I.1.2 La rétine

La rétine qui est formée de multiples couches cellulaires se situe entre l'humeur vitrée et l'épithélium pigmentaire sous-choroïdal. Elle s'étend de la papille jusqu'à l'ora serrata. On y retrouve 3 zones d'intérêt : la macula, la fovéa et la papille. La macula est la région centrale de la rétine et elle se compose en grande partie de cônes qui sont responsables de la vision des couleurs. Au centre de la macula, on retrouve la fovéa, composée exclusivement de cônes hautement concentrés, et alors responsable de la vision la plus précise où l'acuité visuelle (AV) est à son apogée. Enfin, la papille est la région dépourvue de photorécepteurs d'où émerge le nerf optique.
Soulignons la couche profonde de la rétine, l'épithélium pigmentaire rétinien, qui constitue une couche basale visant à assurer les besoins métaboliques des cellules rétiniennes.

I.1.3. La choroïde

La choroïde est la tunique vasculaire du globe oculaire qui s'étend des corps ciliaires jusqu'au nerf optique. Cette couche vascularise la portion externe de la rétine.

I.1.4 La sclérotique

La sclérotique est la structure blanchâtre qui recouvre une grande partie externe de l'œil. Constituée en grande partie de tissu conjonctif résistant et peu vascularisé, elle assure la protection des composantes internes de l'œil, contient la pression intraoculaire et donne la forme oculaire ronde.

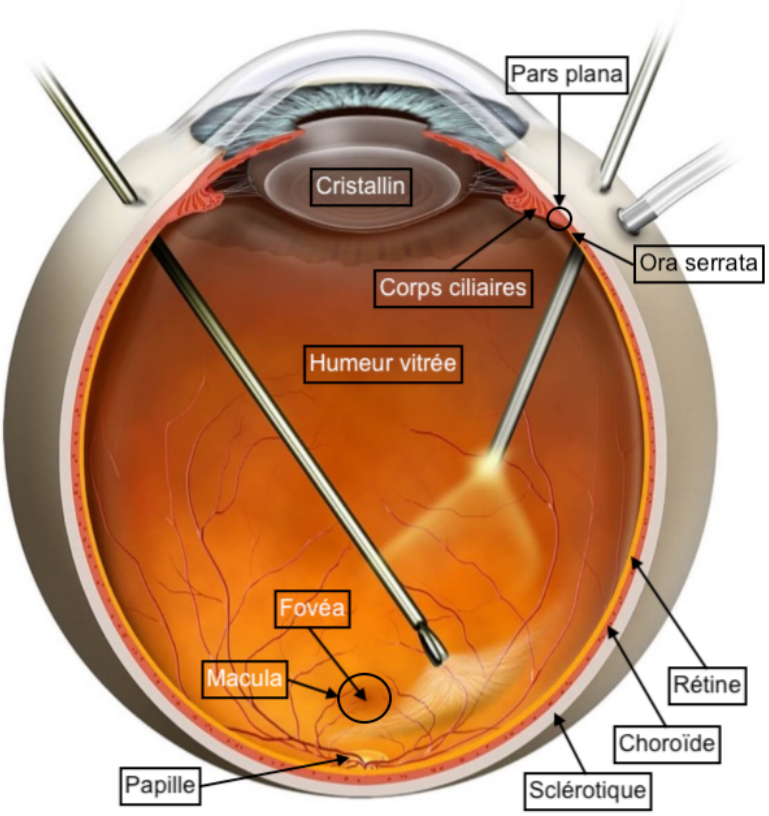

Figure I.1. Représentation schématique de l'œil lors d'une vitrectomie, figure adaptée de : Eyecre.at. https://www.eyecre.at/vitrectomy/ (consulté le 12 août 2021).

I.2. Approche clinique en ophtalmologie : échelles pour l'acuité visuelle

L'AV est la mesure de la fonction visuelle à une distance donnée et à un contraste élevé. Toutefois, celle-ci ne renseigne pas sur la capacité de voir et distinguer les couleurs ou encore les contrastes. Au fil des années, des échelles d'AV se sont développées, au départ, sans souci de standardisation. Ces échelles sont utilisées principalement pour évaluer les erreurs de réfraction, suivre l'évolution de maladies oculaires et quantifier l'efficacité de traitements ophtalmologiques [2]. Il est crucial de comprendre ces échelles d'AV puisqu'elles permettent notamment d'évaluer le niveau de succès d'une intervention chirurgicale oculaire comme la vitrectomie. L'échelle de Snellen et ETDRS sont les deux plus utilisées en clinique et en recherche.

I.2.1 Échelle de Snellen

L'échelle de Snellen **(Annexe A)** est un graphique composé de lettres qui permet d'obtenir une AV selon l'angle visuel permettant de distinguer les lettres. Le graphique est lu à une distance de 6 mètres (ou 20 pieds), et ce, un œil à la fois. Par exemple, une AV à 20/40 signifie que la personne peut lire à 20 pieds ce qu'une personne normale devrait lire à 40 pieds. La distance réelle est à 20 pieds et le dénominateur indique la taille relative de la lettre, généralement selon la distance à laquelle la largeur de trait sous-tendrait un angle visuel de 1 minute; dans ce cas-ci, l'angle visuel serait de 1 minute d'arc à 40 pieds.

Chaque ligne du graphique comporte un nombre de lettres différent, soit entre 1 et 8 lettres. Par exemple, une amélioration d'AV de 3 lettres lues ne signifie pas la même amélioration selon la ligne puisque chaque ligne comporte un nombre de lettres différent. Autrement dit, un gain de 3 lettres représente une plus grande amélioration sur la ligne correspondant à une AV de 20/70 comparativement à la ligne 20/20. Également, la diminution de la grosseur des lettres entre chaque ligne est irrégulière et arbitraire. Enfin, une lettre par rapport à une autre n'a pas toujours la même lisibilité. Par exemple, le « C », « O » et « Q » sont difficiles à différencier alors que le « A », « H » et « T » sont très différents et alors plus faciles à différencier [3]. Selon certaines études, l'échelle de Snellen serait moins précise pour des patients avec des AV plus faibles [4]. Également, la variabilité test-retest liée à cette échelle semble importante, soit ± 16,5 lettres chez les sujets normaux et jusqu'à 3,3 lignes chez des patients pseudophaques, présentant des cataractes ou atteints à un stade précoce de

glaucome [5, 6]. Ainsi, un changement d'AV peut être attribuable au hasard sans véritable effet en lien avec une détérioration/amélioration de l'état de santé. De plus, la distance entre les lignes et les lettres varie considérablement, ce qui crée un phénomène d'encombrement du contour adjacent des caractères. En d'autres mots, plus les lettres sont espacées, plus le phénomène d'encombrement est important, ce qui réduit l'AV. Par conséquent, les lignes associées à une meilleure AV ont un phénomène d'encombrement plus élevé que celles associées aux AV moins bonnes [7].

I.2.2 Échelle Early Treatment Diabetic Retinopathy Study (ETDRS)

Le test d'AV avec l'échelle ETDRS a été conçu pour évaluer les changements de vision à la suite de traitements chez les patients atteints de rétinopathie diabétique. Le graphique ETDRS (**Annexe B**) quant à lui comporte le même nombre de lettres sur chaque ligne (5 lettres) et l'espacement entre les caractères et les lignes est uniforme. La progression dans la taille des lettres est elle aussi uniforme et non arbitraire. En effet, la progression dans la taille des lettres d'une ligne à une autre suit une progression logarithmique; 0,1 logMAR (MAR : angle minimal de résolution). Ainsi, une progression constante fait en sorte qu'on peut ajuster la distance entre le sujet et le graphique en corrigeant la distance avec un certain facteur. Tout de même, il a été déterminé qu'avec l'échelle ETDRS, le patient lira les lettres à une distance de 2 mètres (ou 6,5 pieds) ou à 4 mètres (ou 13 pieds) pour des fins pratiques [7].

Comparativement à l'échelle de Snellen, l'échelle ETDRS donne de meilleurs résultats d'AV lorsque l'AV est faible. En effet, une étude a répertorié que les yeux avec une AV à 20/160 ou moins bonne avaient en moyenne +12,6 lettres aux tests avec l'échelle ETDRS par rapport à l'échelle de Snellen ($p<0,05$). Pour les yeux ayant une bonne AV (20/25 ou mieux), la différence entre les graphiques de Snellen et ETDRS était en moyenne de +1,9 lettre de mieux aux tests avec l'échelle ETDRS comparativement à l'échelle de Snellen ($p<0,05$) [8]. En ce qui concerne la variabilité test-retest, elle a été déterminée à environ ± 10 lettres chez des sujets sains, ce qui est moins important que dans l'échelle de Snellen [9]. Selon une étude de Shamir et al., grâce à une analyse globale ainsi qu'une analyse de sous-groupe (AV faible, modérée et élevée), la reproductibilité et la précision étaient meilleures pour le graphique ETDRS par rapport à l'échelle de Snellen [4]. Bref, l'échelle ETDRS a été validée et elle est reconnue comme étant précise et fiable [10].

Pour toutes ces raisons, l'échelle ETDRS est reconnue aujourd'hui comme le « gold standard » pour mesurer l'AV en recherche; surtout dans le domaine de la rétine. Néanmoins, l'échelle de Snellen demeure souvent plus utilisée en clinique pour des raisons de rapidité et de coût. En effet, il serait deux fois plus rapide d'administrer un test avec l'échelle de Snellen que ETDRS [6]. Il existe également plusieurs graphiques ETDRS avec des changements mineurs en fonction des pays notamment. Par exemple, la police d'écriture peut changer.

De plus, on ne peut pas faire de calculs statistiques avec les fractions d'AV de l'échelle Snellen. À des fins pratiques, une formule mathématique a été déterminée afin de convertir des fractions d'AV de l'échelle de Snellen à l'échelle ETDRS pour pouvoir manipuler plus facilement des résultats dans des calculs statistiques (AV LogMAR = -log(AV Snellen en décimal). AV avec l'échelle ETDRS = 85+50(-(AV logMAR))) [11].

Enfin, expliquons davantage ce qu'est le logMAR puisque cette unité de mesure est énormément utilisée en recherche à des fins statistiques pour les calculs de moyenne d'AV et d'écart-type dans une population d'yeux. Le MAR (angle minimal de résolution) est la taille angulaire minimale permettant de distinguer des lettres sur test d'AV. Cette échelle permet d'obtenir une progression linéaire dans l'AV pour pallier la progression géométrique avec les échelles d'AV. Le MAR est l'inverse de la notation décimale de l'échelle de Snellen. Par exemple, 6/60 à l'échelle de Snellen équivaut à un MAR de 10. Par la suite, comme la progression des MAR est elle aussi géométrique et non arithmétique, ceci empêche tout calcul de moyenne ou d'écart-type. Donc, on utilise le logMAR qui permet d'obtenir une progression linéaire [12].

I.3 Les trous maculaires

Le trou maculaire (TM) idiopathique de pleine épaisseur est un défaut de toutes les couches de la fovéa. Cette zone est responsable de la vision la plus précise et un défaut au sein de celle-ci entraîne une diminution de l'AV et une métamorphopsie.

Sa prévalence varie grandement dans la littérature selon les études. Elle est de 0,33% dans une étude réalisée aux États-Unis [13], 0,02% dans une étude de l'Australie [14], 0,09% dans une étude de Pékin [15] et 0,17% dans une étude dans le sud de l'Inde [16]. La plus large étude réalisée, Beaver Dam Eye Study, a noté une prévalence de 0,3% dans la population aux États-Unis ; le risque augmente selon l'âge avec une prévalence de 0,7% chez les personnes de 75 ans et plus [17]. L'incidence des TM a été étudiée au Minnesota (États-Unis) et selon McCannel et al., elle est de 10,9/100 000 personnes par an (0,0109%) chez les femmes et 4,3/100 000 personnes par an (0,0043%) chez les hommes. L'incidence est alors plus élevée chez les femmes; on considère qu'il y a une prépondérance féminine dans un ratio de 2 : 1 [18]. Les facteurs de risque reconnus à ce jour pour le TM idiopathique sont l'âge de plus de 64 ans et le sexe féminin [19-21].

L'étiologie du TM est principalement idiopathique bien qu'il existe également des TM liés à d'autres causes. Par exemple, il existe des TM traumatiques, des TM associés à une forte myopie, à la dégénérescence maculaire liée à l'âge ou encore à des télangiectasies maculaires de type 2 [22].

Le TM idiopathique de pleine épaisseur résulte de changements à l'interface vitréomaculaire. Le mécanisme n'est pas encore clair, mais avec l'émergence de la tomographie par cohérence optique (OCT), le processus de décollement du vitré postérieur a été mis en évidence. Avant l'apparition de ce décollement du vitré postérieur, des changements discrets surviennent dans le tissu fovéal. On s'entend pour dire que la formation des TM résulte de la traction vitréenne, de la contraction du cortex vitréen et de la formation d'un kyste fovéal [23, 24]. Néanmoins, la raison du décollement de l'hyaloïde postérieure reste incertaine [25].

Une classification des TM a été proposée par Gass et al. en 1988 [26]. Cette classification était basée à l'époque sur des observations biomicroscopiques à l'aide de la lampe à fente sans l'appui de l'OCT, ce qui fait en sorte que la classification a dû être ajustée avec l'avènement de l'OCT. Notamment, un stade 0 a été ajouté à la classification puisque l'OCT a permis de détecter qu'avant l'apparition du TM, des changements morphologiques dans la rétine étaient présents, c'est-à-dire un détachement périfovéolaire de l'hyaloïde postérieure avec une fovéa normale ou encore des atteintes mineures du contour de la fovéa ou de la réflectivité. Dans le stade 1A, il y a un décollement périfovéolaire de l'hyaloïde

postérieure ainsi qu'un kyste dans la fovéa interne et/ou un décollement de la fovéa de la ligne des extrémités du segment externe du cône. Dans le stade 1B, il y a un décollement périfovéolaire de l'hyaloïde postérieure ainsi qu'un kyste fovéal s'étendant jusque dans la couche externe de photorécepteurs de la rétine. Dans le stade 2, il y a une ouverture partielle du toit du kyste fovéal (largeur du TM <400 µm au stade 2), mais sans perte complète de tissu rétinien fovéolaire. Dans le stade 3, l'hyaloïde postérieure est détachée de la surface maculaire, mais toujours attachée au disque optique (largeur du TM > 400 µm). Dans le stade 4, il y a un décollement postérieur complet du vitré et l'hyaloïde postérieure n'est pas visible à l'OCT [26-30].

I.3.1 Traitement du trou maculaire

Le traitement du TM repose principalement sur une vitrectomie par la pars plana (VPP) dans laquelle le vitré est retiré et remplacé par une tamponnade (SF_6, C_3F_8, air ou huile de silicone) (**Figure I.2**) [31]. L'objectif de cette chirurgie est de relâcher la traction exercée notamment par les membranes vitréennes sur la fovéa afin de permettre au tissu glial de combler et fermer le TM. Le rôle le plus probable des tamponnades gazeuses est que la bulle de gaz agit d'abord en déshydratant le rebord du TM puis empêche les courants de fluide du vitré d'entraver le processus de guérison. L'usage de l'huile de silicone est quant à elle réservée pour certains cas plus particuliers (e.g. voyage en avion tôt à la suite de la chirurgie ou difficulté de positionnement adéquat en post-opératoire) [22]. Au fil des années, le pelage de la membrane limitante interne (ILM) a de plus en plus été pratiqué de routine lors de la vitrectomie. Plusieurs études ont évalué l'avantage de pratiquer cette manœuvre adjuvante. Il est maintenant reconnu que le pelage de l'ILM est associé à de plus hauts taux de fermeture des TM ainsi qu'à une amélioration significative de l'AV post-opératoire, et ce, pour les TM de toutes grandeurs confondues [22, 31]. Enfin, après la chirurgie, il est d'usage que le patient soit face contre le sol pour 5 jours en moyenne. L'objectif de ce positionnement est de maintenir la bulle de gaz contre le TM pour éviter les courants de fluide du vitré afin de favoriser la guérison du TM [32].

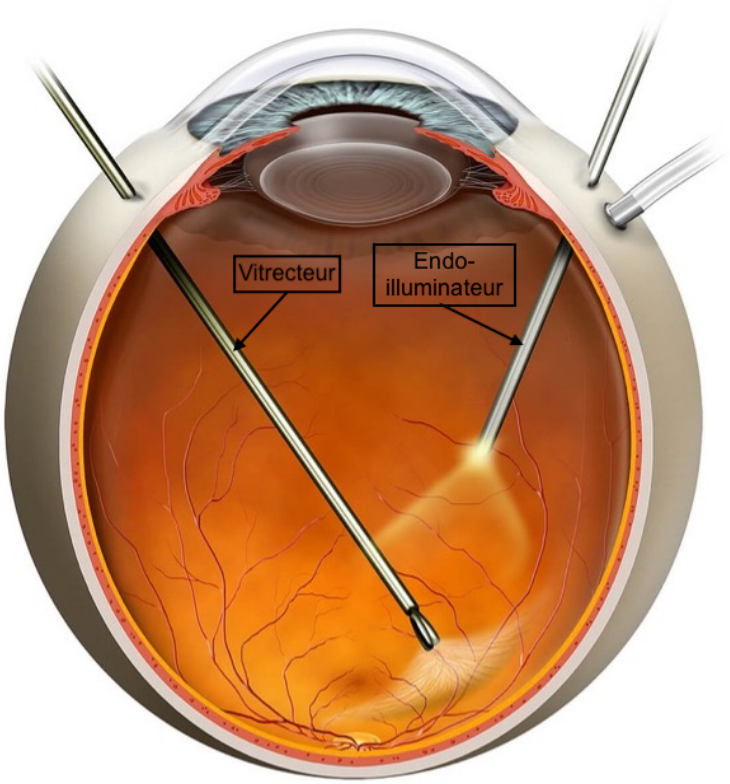

Figure I.2. Vitrectomie par la pars plana : Vitrecteur aspirant le vitré et endo-illuminateur permettant une visualisation optimale, figure adaptée de : Eyecre.at. https://www.eyecre.at/vitrectomy/ (consulté le 12 août 2021).

La VPP comporte peu de complications post-opératoires la plupart du temps, mais les plus rapportées sont le décollement de la rétine, des défauts dans le champ visuel et la réouverture du TM. Il est à noter qu'une chirurgie de la cataracte est très souvent nécessaire à la suite d'une vitrectomie, mais cela ne constitue pas une complication, mais plutôt un effet collatéral. En effet, de 3 à 5 ans après une VPP pour un TM, 85 à 98% des patients sont pseudophaques [33].

La fermeture anatomique ainsi que l'état des différentes couches rétiniennes sont visualisés à l'OCT après la chirurgie (**Figure I.3**). À la suite de ce traitement, la littérature considère le taux de fermeture des TM idiopathiques entre 78% et 96% [34]. Il arrive que des interventions chirurgicales échouent. Les options de prise en charge après l'échec d'une vitrectomie primaire pour un TM idiopathique comprennent l'observation, l'échange de tamponnade et la vitrectomie de révision avec différentes approches au niveau de l'ILM, incluant les greffes de membrane amniotique, le décollement rétinien induit au niveau de la

macula et l'autogreffe rétinienne. La décision d'opter pour l'un de ces choix relève de plusieurs paramètres et d'un consensus avec le patient. À noter que le pronostic des TM non traités n'est pas très bon, c'est-à-dire que seulement 5% des yeux non opérés auront une AV de 20/50 ou mieux 9 ans après le diagnostic [20]. Le chapitre 3 abordera spécifiquement les non-fermetures chirurgicales après une première VPP.

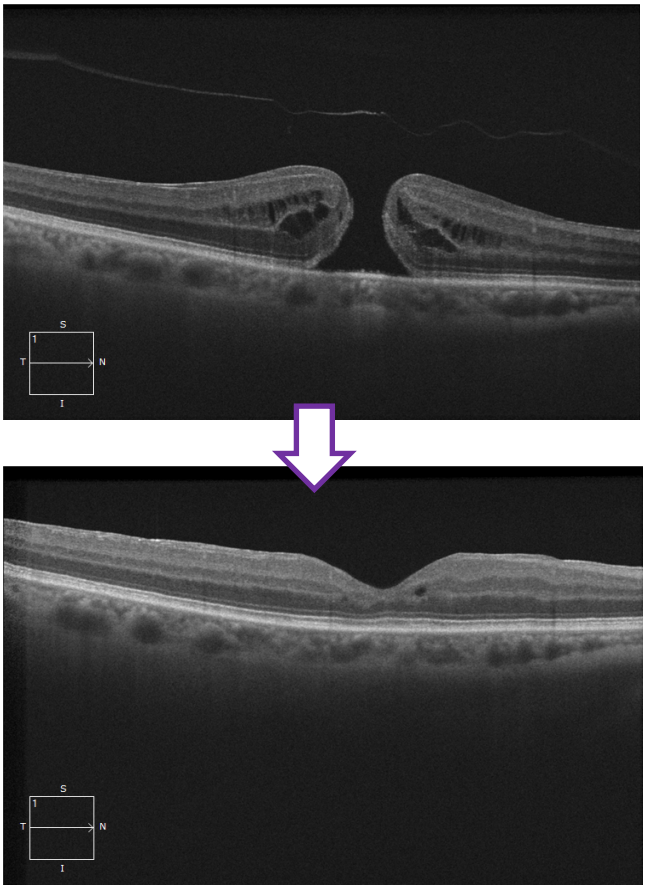

Figure I.3. OCT d'un trou maculaire avant et 24 mois après la VPP.

Bien que non utilisé pour le traitement à proprement dit du TM, le médicament Jetrea™ (ocriplasmine) a longtemps été utilisé pour traiter la traction vitréo-maculaire symptomatique précédant souvent l'apparition du TM. Il a aussi été utilisé lors de l'association de traction vitréo-maculaire avec un TM de moins de 400µm. Le Jetrea™ agit en séparant le vitré de la macula par dissolution des protéines impliquées dans la traction, ce qui libère ladite traction exercée sur la rétine [35].

I.4 La tomographie par cohérence optique

L'OCT est la méthode de référence pour évaluer et suivre un patient atteint d'un TM. Elle permet d'effectuer le diagnostic différentiel avec d'autres pathologies aux symptômes similaires, d'évaluer le pronostic du patient et d'assurer un suivi. Cette méthode d'imagerie apporte une analyse qualitative (morphologie globale du TM) et quantitative (diamètre et volume du TM) de la structure rétinienne [36]. De plus, depuis l'apparition en clinique des OCT, beaucoup d'études ont été mises en place pour diverses pathologies rétiniennes, dont les TM, afin de déterminer la corrélation entre l'atteinte de certaines structures rétiniennes et l'AV. Jusqu'à présent dans la littérature, c'est l'intégrité de la membrane limitante externe (ELM) et de la zone ellipsoïde (EZ) en post-opératoire qui sont les deux structures importantes corrélées à l'AV suivant une VPP [37,38]. Ceci renforce d'autant plus l'idée que la fermeture anatomique n'est pas l'unique élément responsable d'une AV post-opératoire satisfaisante puisqu'un TM peut être complètement fermé, mais posséder des disruptions dans différentes couches rétiniennes.

L'OCT est une technique d'imagerie non-invasive qui utilise des faisceaux lumineux à faible fréquence sur le tissu cible. Lorsque la lumière frappe la rétine, celle-ci peut être absorbée, diffusée ou réfléchie, ce qui permettra d'avoir l'aspect multicouche de la rétine. La lumière rétro-réfléchie est comparée à un deuxième faisceau lumineux de référence. Chaque interférence créée le long d'un faisceau lumineux qui traverse le tissu forme une série de A-scan axial; l'interférence est convertie en niveaux de gris, où le blanc représente le maximum de réflectivité et le noir le minimum de réflectivité. À partir de tous ces A-scans, une coupe transversale bidimensionnelle est reconstituée, ce qu'on appelle le B-scan. La vitesse de balayage de l'instrument, soit la vitesse d'acquisition des A-scans par seconde, est cruciale pour la quantité de données contenue dans l'OCT. Actuellement, l'appareil largement utilisé HD-OCT (haute définition-OCT) permet l'acquisition jusqu'à 68 000 A-scans par seconde [39].

L'enjeu majeur des OCT est la gestion du bruit sur l'image, responsable de l'aspect granulaire. Une réduction trop importante du bruit amène à la perte d'une visualisation adéquate des différentes structures de la rétine. Il est alors crucial de réduire le bruit dans une bonne proportion pour conserver l'aspect des différentes structures. On peut réduire ce bruit grâce à la combinaison d'un vaste échantillonnage d'image B-scan positionné de façon

similaire sur la fovéa. Également, on peut réduire les artéfacts sur l'OCT associés aux mouvements des yeux avec une plus courte durée d'acquisition des A-scans [39].

I.4.1 Anatomie rétinienne normale sur l'OCT

La première couche visible sur l'OCT, bien que très subtile, est la membrane limitante interne (1.ILM). Par la suite, on aperçoit la couche de fibres nerveuses (2.NFL), la couche de cellules ganglionnaires (3.GCL), la couche plexiforme interne (4.IPL), la couche nucléaire interne (5.INL), la couche plexiforme externe (6.OPL) et la couche nucléaire externe (7.ONL). Les couches plexiformes sont considérées hyper-réfléchissantes tandis que la couche de cellules ganglionnaires et les couches nucléaires sont hypo-réfléchissantes. On aperçoit également le vitré postérieur (Posterior Vitreous) qui est attaché à la membrane limitante interne.

Dans la rétine externe, on peut apercevoir majoritairement 4 couches, soit la membrane limitante externe (8.ELM), la zone ellipsoïde (9.EZ), la zone d'interdigitation (10.Interdigitation Zone) et l'épithélium pigmentaire rétinien (11.RPE).

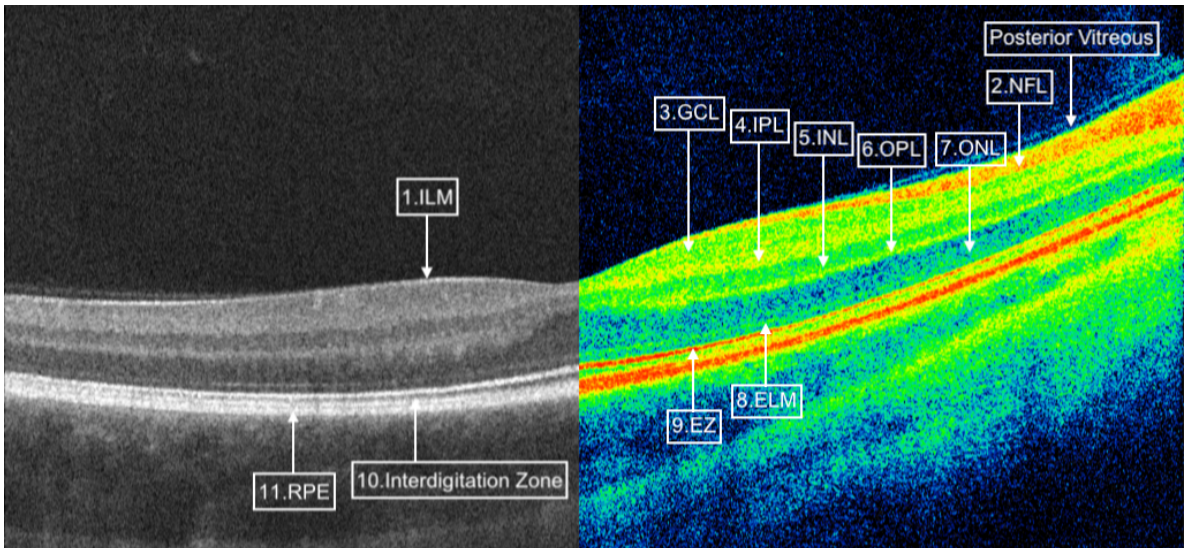

Figure I.4. Schéma d'une OCT modifiée pour illustrer les différentes couches rétiniennes**.** ILM : Internal Limiting Membrane, NFL : Nerve Fiber Layer, GCL : Ganglion Cell Layer, IPL : Inner Plexiform Layer, INL : Inner Nuclear Layer, OPL : Outer Plexiform Layer, ONL : Outer Nuclear Layer, EZ : Ellipsoid Zone, ELM : External Limiting Membrane, RPE : Retinal Pigment Epithelium.

I.5. Enjeux liés aux trous maculaires

Au cours des dernières décennies, il y a eu énormément de progrès sur le plan des techniques chirurgicales en lien avec la VPP. C'est pourquoi le taux de succès, soit de fermeture chirurgicale, d'une première VPP ayant comme indication le TM s'est considérablement accru au fil du temps. Toutefois, plus récemment, on s'aperçoit que malgré un taux de fermeture anatomique élevé, les résultats visuels après l'intervention chirurgicale ne sont pas aussi importants. Dans une vaste étude d'Essex et al., environ le tiers des patients avaient une AV qui ne s'est pas améliorée de manière substantielle dans les TM fermés et même certains yeux n'ont eu aucune amélioration; 32% des yeux (n = 147) se sont améliorés de moins de 15 lettres ETDRS à 24 mois. Dans tous les TM fermés à 24 mois (n = 43), l'AV finale était inférieure à 70 lettres ETDRS dans 29% des cas [40]. Ainsi, cela démontre bien l'importance et la nécessité d'investiguer les facteurs de bons pronostics visuels des TM ayant fermé chirurgicalement à la suite de la première chirurgie et de tenter de prédire la vision post-opératoire des patients. Peu d'études ont évalué les facteurs associés à l'amélioration de l'AV dans les cas de TM idiopathique opérés avec succès. Il demeure beaucoup d'incertitude concernant ces facteurs et ce sujet sera traité au chapitre 1 de ce mémoire. Le chapitre 2 quant à lui mettra de l'avant la combinaison des facteurs cliniques et anatomiques pour prédire l'AV post-opératoire des patients opérés pour un TM, et ce, à l'aide de l'intelligence artificielle. Enfin, nous approfondirons davantage le sujet dans ce mémoire au chapitre 3 en abordant spécifiquement les TM ayant échoué à la première VPP (non-fermeture chirurgicale) puisqu'il s'agit d'un sujet d'intérêt pour bien prendre en charge ce type de patient, et ce, même si la majorité des yeux ont une fermeture chirurgicale à la première VPP.

Chapitre 1 - Prognostic factors for visual outcomes in closed idiopathic macular holes after vitrectomy: outcomes at 4 years in a monocentric study

1.1 Résumé

OBJECTIF: Identifier les facteurs prédictifs des résultats visuels des yeux avec une chirurgie réussie pour un trou maculaire (TM).

MÉTHODES: Étude rétrospective monocentrique des yeux ayant subi une vitrectomie réussie pour un TM de pleine épaisseur dans un hôpital universitaire tertiaire (CHU de Québec – Université Laval, Québec, Canada) entre 2014 et 2018. Nous avons inclus un seul œil par patient et exclu les yeux avec des comorbidités oculaires concomitantes. Les caractéristiques cliniques et anatomiques des patients ont été recueillies, y compris les données démographiques, la durée du TM, la taille préopératoire du TM, l'acuité visuelle (AV) préopératoire et au dernier suivi. Des régressions logistiques multiples ont été réalisées afin de déterminer les facteurs prédictifs de l'AV ≥70 lettres ETDRS (équivalent Snellen: 20/40) et du gain en AV ≥15 lettres ETDRS au dernier suivi. Les aires sous la courbe (ASC) caractéristique de fonctionnement du récepteur ont été utilisées pour déterminer les performances de chaque modèle et identifier l'indice de Youden maximisant les performances à un seuil donné.

RÉSULTATS: Au total, 460 yeux ont été inclus dans cette étude; 274/460 yeux (60%) ont obtenu une AV finale ≥70 lettres ETDRS et 304/460 yeux (66%) un gain en AV ≥15 lettres ETDRS à 24 mois de suivi. Des analyses de régression logistique multiple ont montré que les principaux facteurs prédictifs d'une AV finale ≥70 lettres ETDRS (ASC du modèle = 0.716) étaient l'AV préopératoire (OR = 1.064; p<0.001), la durée du TM (OR = 0.950; p=0.005) et l'âge (OR = 0.954; p=0.004). Les prédicteurs d'un gain en AV ≥15 lettres ETDRS au suivi final (ASC du modèle = 0.615) étaient l'AV préopératoire (OR = 0.878; p<0.001), la durée du TM (OR = 0.940; p<0.001) et la taille du TM (OR = 0.998; p=0.036). Les seuils pour le modèle de l'AV finale ≥70 ETDRS et pour le modèle du gain en AV ≥15 lettres ETDRS étaient respectivement une AV ≥55,5 lettres ETDRS (équivalent Snellen: 6/30) et une taille du TM de 237 µm.

CONCLUSION: Les yeux avec une durée du TM plus courte, une taille du TM plus petite et une AV préopératoire plus élevée ont obtenu de meilleurs résultats visuels après une chirurgie réussie pour un TM.

1.2 Abstract

PURPOSE: To identify predictive factors of visual outcomes in eyes after successful macular hole (MH) surgery.

METHODS: Retrospective monocentric study of eyes that underwent successful vitrectomy for full-thickness MH in an academic, tertiary care center (CHU de Québec – Université Laval, Québec, Canada) between 2014 and 2018. We included a single eye per patient and excluded eyes with ocular comorbidities. Clinical and anatomical features of patients were collected, including demographics, MH duration, baseline MH size, baseline visual acuity (VA), and final VA. Multiple logistic regressions were performed to determine predictive factors of VA ≥70 ETDRS letters (Snellen equivalent: 20/40) and VA gain ≥15 ETDRS letters at final follow-up. Areas under the receiver operating characteristic curve (AUC) were used to determine the performance of each model and identify the Youden index maximizing performance at a given threshold.

RESULTS: A total of 460 eyes were included in this study; 274/460 eyes (60%) achieved final VA ≥70 ETDRS letters and 304/460 eyes (66%) had a VA gain ≥15 ETDRS letters at 24 months follow-up. Multiple logistic regression analyses showed that the main predictive factors for final VA ≥70 ETDRS letters (model AUC = 0.716) were baseline VA (OR = 1.064; p<0.001), MH duration (OR = 0.950; p=0.005), and age (OR = 0.954; p=0.004). Predictors of VA gain ≥15 ETDRS letters at final follow-up (model AUC = 0.615) were baseline VA (OR = 0.878; p<0.001), MH duration (OR = 0.940; p<0.001), and MH size (OR = 0.998; p=0.036). Thresholds for the final VA ≥70 ETDRS letters model and the VA gain ≥15 ETDRS letters model were VA ≥55.5 ETDRS letters (Snellen equivalent: 6/30) and MH size of 237 µm, respectively.

CONCLUSION: Eyes with shorter MH duration, smaller MH size and higher preoperative VA achieved better visual outcomes after successful MH surgery.

Key words: full-thickness macular hole, idiopathic macular hole, macular hole closure, macular hole surgery, pars plana vitrectomy, predictive factors.

1.3 Page titre

Prognostic factors for visual outcomes in closed idiopathic macular holes after vitrectomy: outcomes at 4 years in a monocentric study

Abbreviated title: Prognostic factors for visual acuity after macular hole surgery

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1.4 Introduction

Optical coherence tomography (OCT) and wield field retinography contributed to the change of the practice of physicians around the world and helped them to proper diagnose, monitor, and treat numerous eye diseases as macular hole (MH) [1,2].

Idiopathic full-thickness MH affects 1 in 250 people and results in significant visual impairment, including reduced visual acuity (VA) and metamorphopsia [3]. Recent studies have reported MH closure rates after a first surgical procedure between 78% and 96% [4-6]. However, anatomical closure does not necessarily translate into visual improvement. In a recent study by Essex et al, final VA was less than 70 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters and improved less than 15 ETDRS letters at 24 months in a third of patients successfully operated for MH [7]. This highlights the importance of assessing visual outcomes in addition to anatomical outcomes.

Previous studies have tried to identify prognostic factors of visual outcomes after successful MH surgery, but the impact of many of these factors remains unclear. Moreover, these studies were multicentric, increasing surgical heterogeneity, and they were limited by small sample sizes and short follow-up periods, which may underestimate final visual outcomes [5,7-8].

The aim of this study is to identify predictive factors for visual outcomes at long-term follow-up in eyes with successful MH closure after vitrectomy.

1.5 Methods

1.5.1 Study Design and Setting

All consecutive patients operated for idiopathic full-thickness MH between 2014 and 2018 at the Centre Hospitalier Universitaire de Québec – Université Laval (Canada) were identified. Eyes were operated on by one of five vitreoretinal surgeons. Patient records were systematically reviewed to identify patients with successful MH closure after primary vitrectomy retrospectively. The primary outcome was final VA ≥70 ETDRS letters (Snellen equivalent: 20/40). The secondary outcome was VA gain ≥15 ETDRS letters by final follow-up. These thresholds were chosen as a VA gain of ≥15 ETDRS letters is considered to represent a clinically significant improvement and has also been shown to correlate with a

clinically meaningful improvement in patient-perceived outcomes whereas achievement of ≥70 ETDRS letters has important quality of life implications, including driving [9].
This study was approved by the Institutional Review Board of the Centre Hospitalier Universitaire de Québec – Université Laval (2021-5371) and adheres to the tenets of the Declaration of Helsinki.

1.5.2 Eligibility Criteria

We reviewed the record of all eyes operated for MH with a pars plana vitrectomy with internal limiting membrane (ILM) peeling using 0.06% trypan blue (TB) dye (VisionBlue™, DORC, Zuidland, Netherlands) or 0.05% diluted indocyanine green (ICG) dye (ICG, Diagnostic Green GmbH, Aschheim-Dornach, Germany), and gas or air tamponade. The type of tamponade used was at the discretion of the surgeon. All patients had been advised to position face-down after surgery for 5 to 7 days. Only patients with an anatomic MH closure confirmed by spectral domain OCT following surgery were included. Exclusion criteria included patients with a follow-up of less than four weeks, history of vitrectomy for any reason, and intraoperative use of a silicone oil tamponade or special techniques (e.g., free flap, inverted flap, retinal autografts). Eyes with stage 1 MH, lamellar MH, MH secondary to other causes (e.g., trauma, age-related macular degeneration (AMD), type 2 macular telangiectasia, retinal detachment) and eyes with ocular comorbidities that could potentially affect VA including high refractive or axial myopia (i.e., ≥6 diopters of myopia or axial length ≥26 millimeters) were excluded. In patients with bilateral MH on initial presentation, only the first eye operated was included.

1.5.3 Data Extraction

The medical records of all patients were systematically reviewed by the main investigator (AL). Preoperative data collected included age, sex, lens status, myopia, MH duration (defined in our study as duration between the first reference and the time of surgery [10]), baseline VA, and MH size on initial presentation. Operative data included surgical technique (i.e., vitrectomy or combined phacovitrectomy), type of dye, and tamponade. Postoperative data included VA at 2 weeks, 3 months, 6 months, 12 months, 24 months, 36 months, and 48 months postoperatively. Lens status was recorded at each visit.

VA were originally recorded on Snellen chart and were converted to ETDRS letters for analysis [11]. Counting fingers was recorded as 10 ETDRS letters. We had no patients with VA of hand motion, light perception, or no light perception.

All OCT scans were performed using the CIRRUS HD-OCT 5000 machine (Carl Zeiss Meditec, Jena, Germany). We evaluated preoperative OCT of all patients included in the study for MH size (measured as the minimum hole width or the narrowest aperture size in the middle retina, as defined by the Vitreomacular Traction Study Group [12]), presence of cystic cavities (defined as the intraretinal space in the foveal wall of the MH), and presence of elevated MH edges (defined as the presence of elevated edges of neurosensory retina in relation to the retinal pigment epithelial plane). We measured the diameter of the MH as defined by the Vitreomacular Traction Study Group [12], and not as the base diameter and height of the wall, since this is more commonly used clinically.

1.5.4 Statistical Analysis

Data are presented as mean ± standard deviation for continuous variables and as frequencies (percentages) for categorical variables. Characteristics and variables were compared between the two final VA groups (i.e., <70 ETDRS and ≥70 ETDRS letters) and between the two final VA gain groups (i.e., <15 ETDRS and ≥15 ETDRS letters). We used independent Student's t-test or Mann-Whitney U test as appropriate for continuous variables and chi-square analysis for categorical variables. Paired t-tests were used to compare continuous variables in the same patient across timepoints. Shapiro-Wilk test and Q-Q plots with 95% confidence intervals were used to test for normal distribution of continuous variables. Collinearity between variables was assessed using Spearman's rank correlation coefficients.

A multiple logistic regression model was built to identify predictive factors of VA ≥70 ETDRS letters and VA gain ≥15 ETDRS letters at final follow-up. These included age, sex, baseline BCVA, MH duration, MH size, tamponade agent used, dye used, bilateral disease, presence of preoperative cystic cavities, presence of preoperative elevated edges of MH, follow-up duration, and pseudophakia at final follow-up. A backwards elimination strategy was used to manually select variables from the full model, with variables $p > 0.2$ removed. Odds ratios (OR) and 95% confidence interval (CI) were calculated for each variable in the final model.

All final models were adjusted for age. Baseline BCVA, MH duration, and MH size were also adjusted for in the final models to identify factors most associated with final VA. For the outcome VA ≥70 ETDRS letters, lens status was summarized using pseudophakia at final follow-up to account for patients who were pseudophakic at baseline and patients who had phacoemulsification during or after MH surgery. For the VA gain outcome, lens status included a variable for pseudophakia at baseline and for phacoemulsification with intraocular lens implantation during or after MH surgery.

Receiver operating characteristic (ROC) curves were used to analyze thresholds in predictive factors for VA ≥70 ETDRS letters and VA gain ≥15 ETDRS letters at final follow-up. The Youden index maximizing sensitivity and specificity for the outcomes are reported along with areas under the ROC curve (AUC).

Statistical analyses were performed using R for Windows (version 3.6.3; R Foundation for Statistical Computing) and IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY). Statistical significance was set at $\alpha = 0.05$.

1.6 Results

A total of 460 eyes were included in the study. The mean age was 69 ± 8 years. Of these, 316 (69%) were women and 113 (25%) were pseudophakic eyes. In total, 274/460 eyes (60%) achieved final VA ≥70 ETDRS letters and 304/460 eyes (66%) had a VA gain ≥15 ETDRS letters at 24 months follow-up. **Table 1.1** and **Table 1.2** present baseline, intraoperative, and postoperative characteristics for the former and the latter outcomes, respectively. Pars plana vitrectomy with removal of posterior hyaloid, ILM peeling (after dye usage), and gas or air tamponade was performed in all eyes. Combined phacoemulsification was carried out in only 2 cases.

We assessed baseline characteristics associated with final VA ≥70 ETDRS letters using univariate analysis (**Table 1.1**). The multiple logistic regression analysis (**Table 1.3**) showed that younger age, higher baseline VA, shorter MH duration, MH elevated edge on preoperative OCT, the use of TB dye, pseudophakia at final follow-up visit, and longer duration of follow-up were independent predictors of final VA ≥70 ETDRS letters (all $p<0.05$).

The variable MH size was not an independent predictor of final VA ≥70 ETDRS letters in our study (OR: 0.999, 95% CI: 0.997-1.000; p = 0.140) but was collinear with baseline VA (Spearman's coefficient correlation of -0.568; p<0.001). Thus, patients with smaller MH size tended to have a better baseline VA.

We also assessed baseline characteristics associated with VA gain ≥15 ETDRS letters using univariate analysis (**Table 1.2**). The multiple logistic regression analysis (**Table 1.4**) for predictors of VA gain ≥15 ETDRS letters showed that the independent predictors were worse baseline VA, smaller MH size, shorter MH duration, preoperative pseudophakia, and combined phaco-vitrectomy/phacoemulsification post-vitrectomy (all p<0.05).

Baseline VA, MH duration, and MH size were the three main prognostic factors found for the two functional outcomes. Higher baseline VA resulted in a better final VA result while worse baseline vision was a predictor of better VA gain. Moreover, shorter MH duration and smaller MH size were predictors of better final VA and VA gain. However, smaller MH was not associated with VA gain in univariate analysis; rather, the opposite effect was observed. In our study, younger age, MH elevated edge on preoperative OCT, the use of TB dye, and longer follow-up duration were significant predictors of final VA but not of VA gain ≥15 ETDRS letters.

1.6.1 Visual Acuity Improvement

Mean VA improvement at 2 weeks, 3 months, 6 months, 12 months, 24 months, 36 months, and 48 months was 7 ± 18, 14 ± 13, 15 ± 17, 17 ± 15, 22 ± 14, 23 ± 14, and 21 ± 22 ETDRS letters, respectively. During the 48-months follow-up period, the proportion of pseudophakic eyes increased from 25% (113/460) to 67% (309/460). Long-term functional results were better for the subset of eyes that were pseudophakic at baseline compared to the whole cohort, but the VA improvement over time was similar in both groups. The long-term visual results are shown in **Figure 1.1**.

ROC analysis illustrates the sensitivity and specificity of the model to predict an outcome. For the models predicting VA gain ≥15 ETDRS letters and final VA ≥70 ETDRS letters, the AUC were 0.716 and 0.615, respectively. The Youden index then designates the threshold which maximizes both sensitivity and specificity. It revealed a threshold for baseline VA of

55.5 ETDRS letters to maximize final VA ≥70 ETDRS letters and a threshold for MH size of 237 µm to maximize VA gain ≥15 ETDRS letters. ROC curves are presented in **Figure 1.2.**

1.7 Discussion

While recent advances in MH surgery have improved the rate of anatomical closure, visual outcomes remain suboptimal in some patients [13-15]. Vitreoretinal surgeons have thus focused their attention on factors that may improve visual outcomes.

Several studies have previously reported that preoperative VA was the most important predictor of postoperative visual outcomes [5,16-18]. Eyes with better baseline VA tend to obtain better postoperative final visual outcome, whereas eyes with worse baseline VA generally gain more vision overall [16-18]. Our study is consistent with these findings. We also identified a threshold of 55.5 ETDRS letters (Snellen equivalent: 6/30) as a significant predictor of final VA ≥70 ETDRS letters.

Strengths of our study include the detailed data collection and preoperative OCT analyses, as well as the inclusion of only successful MH surgery cases to identify variables influencing postoperative VA given MH closure. Moreover, total follow-up was longer in our study (i.e., 48 months) compared to most studies with shorter follow-ups that may underestimate final visual potential [7]. Our study also differs from multicentric studies as our data comes from a single hospital center, resulting in less heterogeneity in surgical practices [5,7-8].

An inverse correlation between MH size and postoperative vision eyes is well recognized, with larger diameter holes typically obtaining worse visual outcomes [19-20]. While MH size was not found to be an independent predictor of final VA ≥70 ETDRS letters in our study, this was likely due to collinearity with baseline VA which was a stronger predictor.

Likewise, smaller MH size was an independent predictive factor of VA gain ≥15 ETDRS letters up to 48-months postoperative. Essex et al. identified MH size as an independent predictive factor of VA increase ≥15 ETDRS letters up to 12 months (OR: 0.88, CI: 0.79-0.99; p=0.037) [7]. However, in their study, routine follow-up beyond 12 months was uncommon.

Shorter duration of MH is known to be associated with better visual outcomes as there is better preservation of the macular structure and external limiting membrane (ELM) [21].

Multiple previous studies have evaluated that effect of MH on VA outcomes; these studies were limited to chronic holes and the follow-up was limited to 6 months [16,22]. In a meta-analysis of 11 studies, the average duration of symptoms in the included studies ranged from 5.5 months to 20.5 months [23]. Another study showed that 56% (169/303) of eyes with MH duration of symptoms shorter than 4 months had final VA ≥70 ETDRS letters at a median follow-up of 2.9 months. However, duration of symptoms was not known for 47% (499/1056) of operations in their study compared to only 4% in our study but we did not evaluate the duration of MH using the same definition [8]. We defined MH duration as the duration between the referral date and the surgery which helps to avoid patient recall bias with symptom onset (e.g., floaters or VA drop).
Our results suggest that proceeding quickly to surgery is associated with more favorable outcomes, especially when it is known to have benefits on postoperative VA and is the only modifiable factor unlike MH size and preoperative VA.

There is a lot of interest in identifying OCT parameters for prediction of visual outcomes. The OCT is a tool that has significantly changed the field of ophthalmology since its appearance; it is a reliable tool for monitoring retinal diseases and various OCT biomarkers can be used clinically [24,25]. Minimum diameter of MH (equivalent to MH size) is one of the most studied parameters. Other parameters include hole height and inner segment/outer segment junction defect length as well as ratios such as the macular hole index (MHI) [26]. In our study, we identified the presence of elevated edges on preoperative OCT as a predictive factor of final VA ≥70 ETDRS letters. A recent study by Tao et al. investigated the impact of postoperative hole edge configurations on visual outcomes and found that MH morphologies with extra flaps of tissue (n = 14) had significantly better final VA and postoperative restoration of the ELM than MH without any specific configuration (n = 24) (p=0.012) [26]. However, to our knowledge no studies have looked at elevated MH edge as a preoperative factor. This highlights the need to include more imaging-related preoperative variables alongside clinical data to assess visual prognosis after MH surgery.

Normal aging is associated with loss of photoreceptors and neural elements with gliosis, which may decrease the ability of the retina to restore the ELM and the ellipsoid zone [27]. In our study, younger age was an independent predictor factor for final VA ≥70 ETDRS letters even after excluding AMD and other ocular comorbidities that could potentially affect VA from our cohort. A few studies have found age to be a predictor, although others have

not [5,7-8]. In Essex et al., age was a predictor of VA gain of ≥15 ETDRS letters at 3 months (OR: 0.80, CI: 0.68-0.94; p=0.006) but not at 12 months (OR: 0.96, CI: 0.74-1.24; p=0.75) or 24 months (OR: 0.52, CI: 0.20-1.38; p=0.19) [7]. However, in our study, age was not a predictor of VA gain ≥15 ETDRS letters.

The use of TB dye was a significant predictor of final VA but not of VA gain ≥15 ETDRS letters (p=0.089). Better visual results with TB dye may be due to ICG toxicity on the retina. In vitro, studies using human retinal pigment epithelial cells have demonstrated the toxic effect of ICG dye and illumination [28]. ICG toxicity results in optic nerve atrophy, loss of epiretinal cellular integrity, and cellular toxicity. However, ICG dye appears to be safe when used at the clinically relevant concentration and with short time exposure, although TB showed lower toxicity [29].

MH occur most commonly in an elderly population and vitrectomy very often results in the need for cataract surgery. More than half the patients in our cohort (n=194/347; 56%) were operated for cataracts over the follow-up period. Previous studies have suggested phacovitrectomy to be associated with better gain in VA and reduced health costs. Moreover, phacovitrectomy was not associated with higher rate of complications as compared to sequential vitrectomy and cataract surgery [7,30-31]. In our study, we included variables related to the lens status in all multiple logistic regressions to limit the effect of this confounding variable on other predictive factors.

Improvement in VA after MH surgery depends on photoreceptor restoration [32], which explains why longer follow-up is a predictor of better final VA. However, in our study, mean total follow-up time was not an independent predictive factor of VA gain ≥15 ETDRS letters.

The main limitation was the retrospective nature of the study with variable follow-up durations. Patients who had a follow-up of less than 4 weeks were excluded; these patients generally lived far from the hospital and were followed by a local ophthalmologist after their surgery. There were also several missing VA data after 24 months. However, VA mostly stabilized at 24 months, which minimizes the bias. Moreover, although the multiple logistic regression models adjusted for lens status, the size of its effect (i.e., OR = 3.948) suggests lens status still has a large effect compared to other characteristics specific to macular holes,

thereby limiting the interpretation of the relative weights between lens status and the models' other variables.

Identifying the factors that predict functional outcomes in eyes with anatomic closure may help ophthalmologists to determine factors that affect specifically visual outcomes rather than the anatomic outcomes. This may help clinicians to focus on key outcome predictors for patients and inform them accordingly. This study provides more solid evidence concerning the long-term prognostic factors. This can improve the quality of care by providing more accurate counselling to patients regarding the visual outcomes after macular hole surgery. This allows patients to make better decisions and have realistic postoperative expectations.

In conclusion, we identified preoperative VA, MH duration, and MH size as independent predictors of functional outcomes after MH surgery. We also identified preoperative VA ≥55.5 ETDRS letters (Snellen equivalent: 6/30) as a significant predictor of final VA ≥70 ETDRS letters and MH size of 237 μm as a significant predictor of VA gain ≥15 ETDRS letters. Finally, future studies using big data and artificial intelligence-based methods are needed to provide a more accurate evaluation of prognostic factors of VA after MH surgery.

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1.9 Disclosures

1.9.1 Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

1.9.2 Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

1.9.3 Funding Statement

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1.9.4 Ethics approval

This study was approved by the Institutional Review Board of the Centre Hospitalier Universitaire de Québec – Université Laval (2021-5371) and adheres to the tenets of the Declaration of Helsinki.

1.10 References

[1] Iglicki M, Loewenstein A, Barak A, Schwartz S, Zur D. Outer retinal hyperreflective deposits (ORYD): a new OCT feature in naïve diabetic macular oedema after PPV with ILM peeling. *Br J Ophthalmol*. 2020;104(5):666-671. doi: 10.1136/bjophthalmol-2019-314523.

[2] Tang F, Luenam P, Ran AR, et al. Detection of Diabetic Retinopathy from Ultra-Widefield Scanning Laser Ophthalmoscope Images: A Multicenter Deep Learning Analysis. *Ophthalmol Retina*. 2021;5(11):1097-1106. doi: 10.1016/j.oret.2021.01.013.

[3] Meuer SM, Myers CE, Klein BE, et al. The epidemiology of vitreoretinal interface abnormalities as detected by spectral-domain optical coherence tomography: the beaver dam eye study. *Ophthalmology*. 2015;122:787–95. doi: 10.1016/j.ophtha.2014.10.014.

[4] Yek JTO, Hunyor AP, Campbell WG, McAllister IL, Essex RW. Outcomes of eyes with failed primary surgery for idiopathic macular hole. *Ophthalmol Retina*. 2018; 2(8):757–764. doi: 10.1016/j.oret.2017.10.012.

[5] Fallico M, Jackson TL, Chronopoulos A, et al. Factors predicting normal visual acuity following anatomically successful macular hole surgery. *Acta Ophthalmol*. 2020. doi: 10.1111/aos.14575.

[6] Lachance A, You E, Garneau J, et al. Revision Surgery for Idiopathic Macular Hole after Failed Primary Vitrectomy. *J Ophthalmol*. 2021. doi: 10.1155/2021/8832538.

[7] Essex RW, Hunyor AP, Moreno-Betancur M, et al. Australian and New Zealand Society of Retinal Specialists Macular Hole Study Group. The visual outcomes of macular hole surgery: a registry-based study by the Australian and New Zealand society of retinal specialists. *Ophthalmol Retina*. 2018;2:1143–1151. doi: 10.1016/j.oret.2018.04.022.

[8]. 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. doi: 10.1038/s41433-020-0844-x.

[9] Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci*. 2009;50:3629–3635. doi: 10.1167/iovs.08-3225.

[10] Lumi X, Mahnic M, Petrovski BE, and Petrovski G. Outcomes of Vitrectomy for Long-Duration Macular Hole. *J Clin Med*. 2020; 9(2): 444. doi: 10.3390/jcm9020444.

[11] Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology*. 2007;114:1804e1809. doi: 10.1016/j.ophtha.2007.06.047.

[12] 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. doi: 10.1016/j.ophtha.2013.07.042.

[13] Unsal E, Cubuk MO, and Ciftci F. Preoperative prognostic factors for macular hole surgery: Which is better?. *Oman J Ophthalmol*. 2019:12(1):20–24. doi: 10.4103/ojo.OJO_247_2017.

[14] Bainbridge J, Herbert E, Gregor Z. Macular holes: Vitreoretinal relationships and surgical approaches. *Eye (Lond)*. 2008;22(10):1301-9. doi: 10.1038/eye.2008.23.

[15] Richter-Mueksch S, Sacu S, Osarovsky-Sasin E, Stifter E, Kiss C, Velikay-Parel M. Visual performance 3 years after successful macular hole surgery. *Br J Ophthalmol*. 2009;93(5):660-3. doi: 10.1136/bjo.2008.154963.

[16] Scott RA, Ezra E, West JF, and Gregor ZJ. Visual and anatomical results of surgery for long standing macular holes. *Br J Ophthalmol*. 2000;84(2):150-153. doi: 10.1136/bjo.84.2.150.

[17] Jaycock PD, Bunce C, Xing W, et al. Outcomes of macular hole surgery: implications for surgical management and clinical governance. *Eye (Lond)*. 2005;19(8):879-84. doi: 10.1038/sj.eye.6701679.

[18] Gupta B, Laidlaw DA, Williamson TH, Shah SP, Wong R, Wren S. Predicting visual success in macular hole surgery. *Br J Ophthalmol*. 2009;93(11):1488-91. doi: 10.1136/bjo.2008.153189.

[19] Ezra E, Gregor ZJ, and Morfields Macular Hole Study Group Report No. 1. 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*. 2004;122(2):224-36. doi: 10.1001/archopht.122.2.224.

[20] 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):390-3. doi: 10.1136/bjo.86.4.390.

[21] Kaźmierczak K, Stafiej J, Stachura J, Żuchowski P, Malukiewicz G. Long-Term Anatomic and Functional Outcomes after Macular Hole Surgery. *J Ophthalmol*. 2018:3082194. doi: 10.1155/2018/3082194.

[22] Stec LA, Ross RD, Williams GA, Trese MT, Margherio RR, Cox MS Jr. Vitrectomy for chronic macular holes. *Retina*. 2004;24(3):341-7. doi: 10.1097/00006982-200406000-00001.

[23] Kang HK, Chang AA, and Beaumont PE. The macular hole: report of an Australian surgical series and meta-analysis of the literature. *Clin Exp Ophthalmol*. 2000;28(4):298-308. doi: 10.1046/j.1442-9071.2000.00329.x.

[24] Zur D, Iglicki M, Busch C, Invernizzi A, Mariussi M, Loewenstein A. International Retina Group. OCT Biomarkers as Functional Outcome Predictors in Diabetic Macular Edema Treated with Dexamethasone Implant. *Ophthalmology*. 2018;125(2):267-275. doi: 10.1016/j.ophtha.2017.08.031.

[25] Iglicki M, Lavaque A, Ozimek M, et al. Biomarkers and predictors for functional and anatomic outcomes for small gauge pars plana vitrectomy and peeling of the internal limiting membrane in naïve diabetic macular edema: The VITAL Study. *PLoS One*. 2018;13(7):e0200365. doi: 10.1371/journal.pone.0200365.

[26] Tao J, Chen H, Zhu L, et al. Macular hole edge morphology predicts restoration of postoperative retinal microstructure and functional outcome. *BMC ophthalmol*. 2020;20(1):280. doi: 10.1186/s12886-020-01541-7.

[27] Grossniklaus HE, Nickerson JM, Edelhauser HF, Bergman LA, Berglin L. Anatomic alterations in aging and age-related diseases of the eye. *Invest Ophthalmol Vis Sci*. 2013; 54(14):ORSF23–ORSF27. doi: 10.1167/iovs.13-12711.

[28] Horio N and Horiguchi M. Effect on visual outcome after macular hole surgery when staining the internal limiting membrane with indocyanine green dye. *Arch Ophthalmol*. 2004;122(7):992-6. Doi: 10.1001/archopht.122.7.992.

[29] Shen Y, Zhang L, Zhou H, Wu M. Comparative effects of commonly used intraocular dyes on the viability of human retina Müller cells. *Biomed Pharmacother*. 2020;132:110790. doi: 10.1016/j.biopha.2020.110790.

[30] Simcock PR and Scalia S. Phacovitrectomy without prone posture for full thickness macular holes. *Br J Ophthalmol*. 2001;85:1316–1319. doi: 10.1136/bjo.85.11.1316.

[31] Port AD, Nolan JG, Siegel NH, Chen X, Ness SD, Subramanian ML. Combined phaco-vitrectomy provides lower costs and greater area under the curve vision gains than

sequential vitrectomy and phacoemulsification. *Graefes Arch Clin Exp Ophthalmol*. 2020;259(1):45-52. doi: 10.1007/s00417-020-04877-4.

[32] Mitamura Y, Mitamura-Aizawa S, Katome T, et al. Photoreceptor impairment and restoration on optical coherencetomographic image. *J Ophthalomol*. 2013. doi: 10.1155/2013/518170.

1.11 Tables

Table 1.1. Baseline, Intraoperative, and Postoperative Characteristics in Eyes with Final VA ≥70 ETDRS Letters Versus <70 ETDRS Letters Following Primary Vitrectomy for Idiopathic Full-thickness Macular Hole

Variables	VA ≥70 letters *n*=274	VA <70 letters *n*=186	*P* Value
Preoperative			
Age mean±SD, *years*	67±8	69±8	0.145
Female gender, n (%)	182 (66)	134 (72)	0.223
Pseudophakia, n (%)	67 (25)	46 (25)	1.000
Baseline BCVA mean±SD, *letters*	56±12	44±16	<0.001*
MH duration mean±SD, *weeks*	10±6	13±12	0.001*
MH size, *μm* (range)	314 (50-808)	415 (108-1001)	<0.001*
MH cystic cavities, n (%)	259 (95)	169 (91)	1.000
MH elevated edge, n (%)	242 (88)	156 (84)	0.748
Operative			
Dye			0.061
ICG, n (%)	211 (77)	157 (84)	
TB, n (%)	64 (23)	30 (16)	
Tamponade			0.328
SF_6, n (%)	253 (92)	167 (90)	
C_3F_8, n (%)	21 (8)	20 (11)	
Air, n (%)	1 (0.4)	0 (0)	
Combined phacovitrectomy, n (%)	1 (0.4)	1 (0.5)	1.000
Postoperative			
MH residual cystic cavities, n (%)	1 (0.4)	2 (1)	0.564
Phaco post-vitrectomy, n (%)	141 (52)	53 (29)	<0.001*
Pseudophakia at final FU visit, n (%)	209 (76)	100 (54)	<0.001*
Final VA mean±SD, *letters*	77±4	59±12	<0.001*
Mean total FU, *months*	32	24	<0.001*

BCVA: best-corrected visual acuity, SD: standard deviation, MH: macular hole, ICG: Indocyanine green, TB: trypan blue, phaco post-vitrectomy: phacoemulsification post-vitrectomy, FU: follow-up.
*Statistically significant

Table 1.2. Baseline, Intraoperative, and Postoperative Characteristics in Eyes with increase ≥ 15 ETDRS Letters Following Primary Vitrectomy for Idiopathic Full-thickness Macular Hole Between Baseline and Final Follow-up

Variables	≥15 letters increase *n*=277	<15 letters increase *n*=183	*P* Value
Preoperative			
Age mean±SD, *years*	68±8	68±9	0.499
Female gender, n (%)	193 (70)	123 (67)	0.608
Pseudophakia, n (%)	67 (24)	46 (25)	0.826
Baseline BCVA mean±SD, *letters*	46±15	59±11	<0.001*
MH duration mean±SD, *weeks*	11±10	13±10	0.042*
MH size, *μm* (range)	382 (64-1001)	313 (50-950)	<0.001*
MH cystic cavities, n (%)	262 (95)	164 (90)	0.041*
MH elevated edge, n (%)	246 (89)	152 (83)	0.108
Operative			
Dye			0.098
ICG, n (%)	213 (77)	153 (84)	
TB, n (%)	64 (23)	30 (16)	
Tamponade			0.412
SF_6, n (%)	249 (90)	169 (92)	
C_3F_8, n (%)	27 (10)	14 (8)	
Air, n (%)	1 (0.4)	0 (0)	
Combined phacovitrectomy, n (%)	2 (0.7)	0 (0)	0.523
Postoperative			
MH residual cystic cavities, n (%)	1 (0.4)	2 (1)	1.000
Phaco post-vitrectomy, n (%)	143 (52)	51 (28)	<0.001*
Pseudophakia at final FU visit, n (%)	212 (77)	97 (53)	<0.001*
Final VA mean±SD, *letters*	73±9	64±14	<0.001*
Mean total FU, *months*	30	24	<0.001*

BCVA: best-corrected visual acuity, SD: standard deviation, MH: macular hole, ICG: Indocyanine green, TB: trypan blue, phaco post-vitrectomy: phacoemulsification post-vitrectomy, FU: follow-up.
*Statistically significant

Table 1.3. Multiple Logistic Regression for Final VA ≥70 ETDRS Letters Outcome

Variables	Odds ratio	95% CI	*P* Value
Age, *years*	0.954	0.923-0.984	0.004*
Baseline BCVA, *letters*	1.064	1.040-1.091	<0.001*
MH duration, *weeks*	0.950	0.915-0.983	0.005*
MH size, *μm*	0.999	0.997-1.000	0.140
MH elevated edge	2.721	1.099-6.688	0.029*
TB dye	1.953	1.062-3.693	0.035*
Pseudophakia at final FU visit	3.948	2.174-7.247	<0.001*
Mean total FU, *months*	1.022	1.004-1.043	0.021*

VA: visual acuity, CI: confidence interval, MH: macular hole, TB: trypan blue, FU: follow-up.
*Statistically significant

Table 1.4. Multiple Logistic Regression for VA Increase ≥15 ETDRS Letters Between Baseline and Final Follow-up†

Variables	Odds ratio	95% CI	*P* Value
Age, *years*	0.987	0.955-1.021	0.462
Baseline BCVA, *letters*	0.878	0.847-0.907	<0.001*
MH duration, *weeks*	0.940	0.908-0.971	<0.001*
MH size, *μm*	0.998	0.996-0.999	0.036*
TB dye	1.730	0.927-3.296	0.089
Preoperative pseudophakia	2.932	1.489-5.898	0.002*
Combined phaco-vitrectomy or phaco-IOL post-vitrectomy	4.866	2.700-8.989	<0.001*

BCVA: best-corrected visual acuity, VA: visual acuity, CI: confidence interval, MH: macular hole, TB: trypan blue, phaco-IOL: phacoemulsification with intraocular lens implantation.

†Adjusted for bilateral disease and cystic cavities variables
*Statistically significant

1.12 Figures

Figure 1.1. Long-term visual results after MH surgery for final VA ≥70 ETDRS letters and VA gain ≥15 ETDRS letters

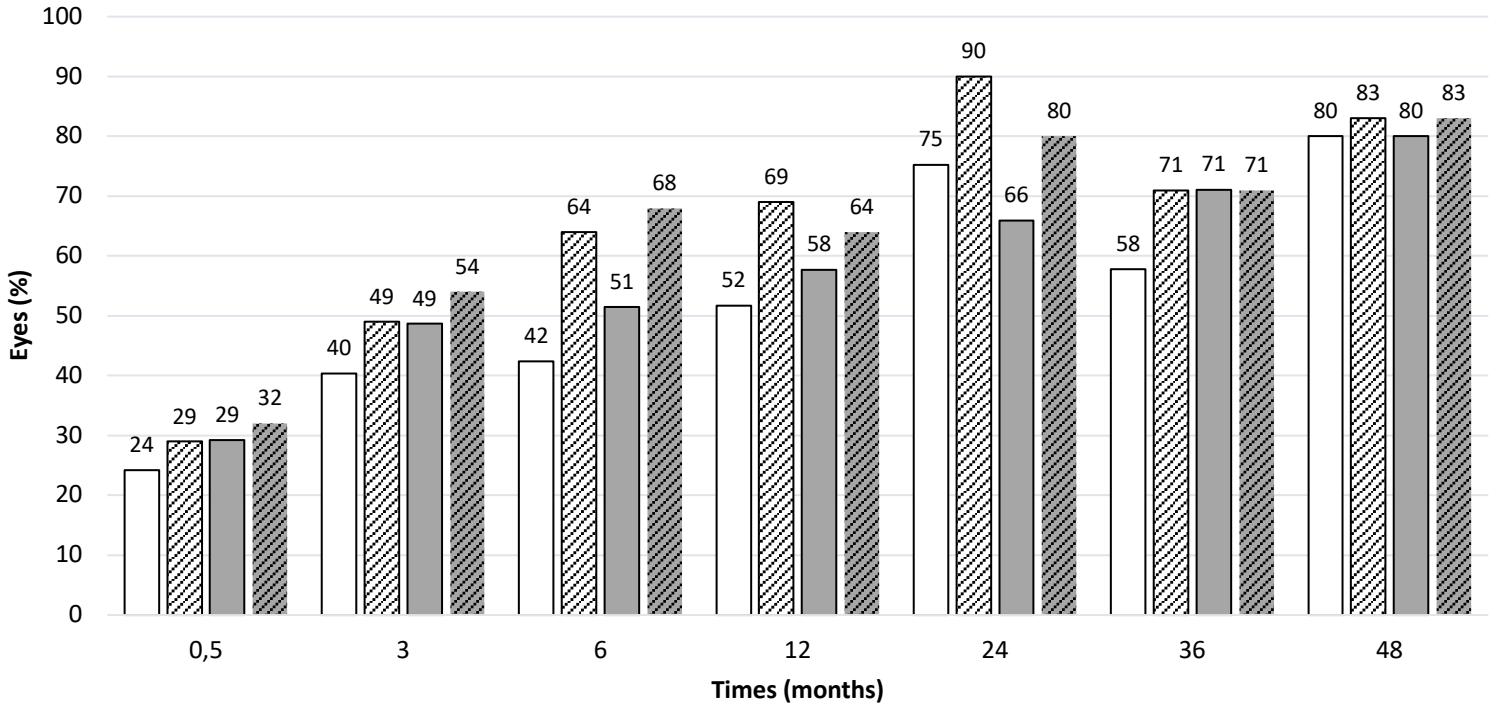
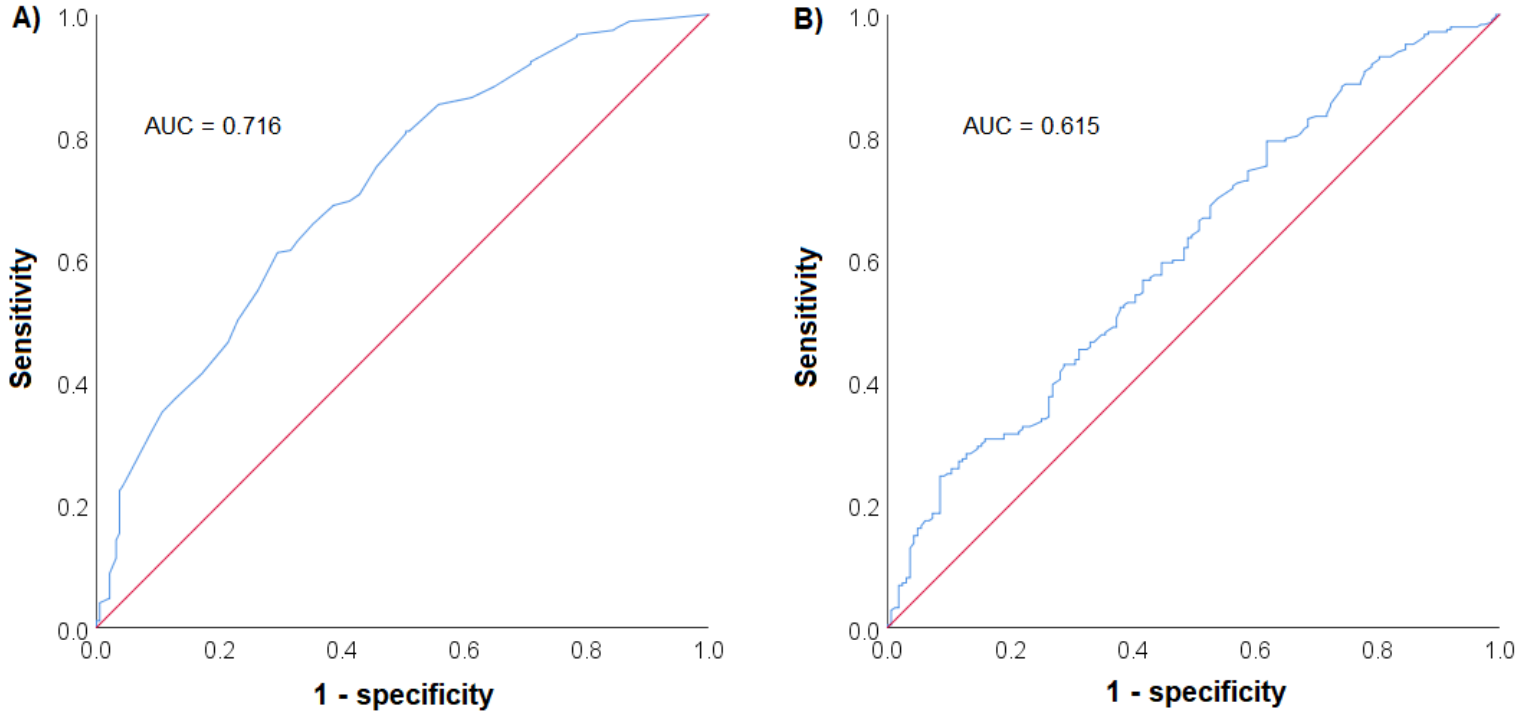


FIGURE LEGEND

- BCVA ≥70 ETDRS letters (whole cohort)
- BCVA ≥70 ETDRS letters (baseline pseudophakic eyes)
- ≥15 ETDRS letters increase in acuity (whole cohort)
- ≥15 ETDRS letters increase in acuity (baseline pseudophakic eyes)

Figure 1.2. ROC curves for visual outcomes



A) Baseline BCVA for ≥70 ETDRS letters at last follow-up
B) MH size for VA gain ≥15 ETDRS letters between baseline and final follow-up

Chapitre 2 - Predicting visual improvement after macular hole surgery: a combined model using deep learning and clinical features

2.1 Résumé

OBJECTIF: Évaluer la faisabilité des méthodes d'apprentissage profond (AP) pour améliorer la prédiction de l'amélioration de l'acuité visuelle (AV) après une chirurgie du trou maculaire (TM) à partir d'un modèle combiné utilisant l'AP sur des B-scans de tomographie par cohérence optique haute définition (HD-OCT) et des caractéristiques cliniques.

MÉTHODES: Nous avons développé un réseau neuronal convolutif (RNC) d'AP à l'aide de B-scans HD-OCT préopératoires de la macula et combiné à un modèle de régression logistique des caractéristiques cliniques pour prédire une augmentation de l'AV ≥15 lettres ETDRS à 6 mois après une vitrectomie réussie pour un TM. Un total de 121 TM avec 242 B-scans HD-OCT et 484 points de données cliniques ont été utilisés pour entraîner, valider et tester le modèle. La prédiction de l'augmentation de l'AV a été évaluée en utilisant l'aire sous la courbe (ASC) caractéristique de fonctionnement du récepteur et les scores F1. Nous avons également extrait le poids de chaque caractéristique d'entrée dans le modèle hybride basé sur la régression.

RÉSULTATS: Toutes les performances sont rapportées sur l'ensemble des tests effectués, correspondant aux résultats obtenus avec la validation croisée. En utilisant une régression sur les caractéristiques cliniques, l'ASC était de 80.6, avec un score F1 de 79.7. Pour le RNC, reposant uniquement sur les images d'OCT préopératoire, l'ASC était de 72.8 ± 14.6, avec un score F1 de 61.5 ± 23.7. Pour notre modèle de régression hybride utilisant les caractéristiques cliniques et la prédiction du RNC, l'ASC était de 81.9 ± 5.2, avec un score F1 de 80.4 ± 7.7. Dans le modèle hybride, l'AV préopératoire était la caractéristique la plus importante (poids: 59.1 ± 6.9 %), tandis que la prédiction des images HD-OCT préopératoires pour la prédiction représentait 9.6 ± 4.2 %.

CONCLUSION: Les données cliniques et les modèles HD-OCT peuvent prédire l'amélioration de l'AV postopératoire chez les patients subissant une vitrectomie pour un TM avec de bonnes performances discriminantes. La combinaison des deux modèles dans un modèle hybride a donné des performances légèrement meilleures, bien que l'amélioration n'ait pas été statistiquement significative.

Pertinence translationelle: Les modèles d'AP basés sur l'OCT peuvent prédire l'amélioration de l'AV postopératoire après une vitrectomie pour TM, mais la fusion de ces modèles avec des données cliniques pourrait ne pas fournir de meilleures performances prédictives.

2.2 Abstract

PURPOSE: The purpose of this study was to assess the feasibility of deep learning (DL) methods to enhance the prediction of visual acuity (VA) improvement after macular hole (MH) surgery from a combined model using DL on high-definition optical coherence tomography (HD-OCT) B-scans and clinical features.

METHODS: We trained a DL convolutional neural network (CNN) using preoperative HD-OCT B-scans of the macula and combined with a logistic regression model of preoperative clinical features to predict VA increase ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 6 months post-vitrectomy in closed MHs. A total of 121 MHs with 242 HD-OCT B-scans and 484 clinical data points were used to train, validate and test the model. Prediction of VA increase was evaluated using the area under the receiver operating characteristic curve (AUROC) and F1 scores. We also extracted the weight of each input feature in the hybrid model.

RESULTS: All performances are reported on the held-out test set, matching results obtained with cross-validation. Using a regression on clinical features, the AUROC was 80.6, with an F1 score of 79.7. For the CNN, relying solely on the HD-OCT B-scans, the AUROC was 72.8±14.6, with an F1 score of 61.5±23.7. For our hybrid regression model using clinical features and CNN prediction, the AUROC was 81.9±5.2, with an F1 score of 80.4±7.7. In the hybrid model, the baseline VA was the most important feature (weight: 59.1±6.9%), while the weight of HD-OCT prediction was 9.6±4.2%.

CONCLUSION: Both the clinical data and HD-OCT models can predict postoperative VA improvement in patients undergoing vitrectomy for a MH with good discriminative performances. Combining them into a hybrid model did not significantly improve performance.

Translational Relevance: OCT-based DL models can predict postoperative VA improvement following vitrectomy for MH but fusing those models with clinical data might not provide improved predictive performance.

Key words: artificial intelligence, visual acuity improvement, vitrectomy, macular hole

2.3 Page titre

Predicting visual improvement after macular hole surgery: a combined model using deep learning and clinical features

Abbreviated title: Predicting visual improvement after macular hole surgery

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2.4 Introduction

Idiopathic full-thickness macular hole (MH) is a discontinuation of the neurosensory retina at the fovea and results in significant visual impairment including reduced visual acuity (VA) and metamorphopsia [1]. Analysis of baseline optical coherence tomography (OCT) in patients with a MH can provide insight into surgical success and postoperative VA [1]. OCT is commonly used in ophthalmology for multiple reasons: it allows noncontact, noninvasive, and easy-to-use cross-sectional images for clinical staging of various retinal diseases including MH by showing foveal and vitreous microstructures.

Pars plana vitrectomy with internal limiting membrane (ILM) peeling is commonly used to treat MH, with recent studies reporting the MH closure rate after a primary surgical procedure between 78% and 96% [1-3]. Despite the high closure rate, functional outcomes after successful surgery are variable [4]. Several authors tried to predict visual outcomes in closed MH based on clinical and imaging factors (e.g. MH duration, preoperative VA, and MH size) or more specific OCT-defined parameters, such as macular hole index (MHI) [2,4,5]. Unfortunately, current predictive methods have some limitations that can cause inaccuracy and variability. For instance, preoperative VA measurement is not always well standardized, MH duration based on symptoms onset is affected by recall bias and subjectivity, and OCT-based MH size and index ratios do not account perfectly for the hole asymmetry and overall hole shape. Moreover, measuring MH dimensions from OCT is time-consuming and requires expertise.

Therefore, other authors tried to predict visual outcomes in closed MH with automated three-dimensional (3D) analyses using preoperative OCT B-scans to measure parameters, such as the base area, maximum base diameter, top area, maximum top diameter, minimum diameter, height, and the MHI [6-8]. Despite its high predictive potential, using a 3D analysis instead of the traditional slice-based analysis suffers from some issues. Namely, modern scanners, such as the Cirrus high-definition (HD)-OCT (ZEISS, Dublin, CA), require 2 seconds to image a target cube. During this period, misalignment across slices can occur due to natural and involuntary movements of the subject's eyes [9]. Although some eye motion correction in 3D-OCT B-scans exists, these inter-slice distortions and misalignments are a significant barrier to a full 3D analysis. Moreover, typically, macular cubes for 3D analysis (512 x 128 pixels) have lower resolution than traditional 2D OCT B-scans (750 x

500 pixels) using Cirrus 5000 HD-OCT, which gives less potential to increase neural network performances. In addition, clinicians routinely examine the OCT B-sans in a slice-by-slice manner. Thus, the ability to analyze and display information about MH in a slice-based manner is aligned with current clinical practices.

Promising deep learning (DL) models have been successfully applied to OCT B-scans to detect various ocular diseases including diabetic retinopathy (DR), age-related macular degeneration (AMD), and MH [10,11]. DL systems have also been used to predict antivascular endothelial growth factor treatment outcomes from pretreatment clinical images, showcasing their ability to also make predictions on the efficiency of a treatment from pretreatment knowledge [12]. Because visual outcomes in MH are affected by both morphological factors on OCT B-scans and other clinical factors, a hybrid model combining these is potentially helpful in predicting postoperative visual improvement.

This study aimed to assess the feasibility of DL methods to enhance the prediction of corrected visual acuity (CVA) increase at 6 months of ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in closed MH after vitrectomy, by using preoperative high-definition (HD)-OCT B-scans in addition to clinical data. To the best of our knowledge, this is the first time a combined model using DL and clinical features is used to try to predict visual outcomes in a closed MH.

2.5 Methods

The chosen clinical ground truth was an improvement of ≥15 letters on ETDRS VA chart 6 months postoperatively. This threshold was previously considered to represent a clinically significant improvement in VA [13]. We formulate this as a classification problem, where the DL model is asked to predict a binary outcome, that is whether CVA will improve by ≥15 letters 6 months after surgery. Predicting the precise number of letters gained postoperatively is subject to too much variation and instability, and has less interesting clinical implications (i.e. a CVA gain of 5 instead of 6 letters is not clinically significant). CVA was defined here as the best VA obtained using the patient's current refractive correction with or without pinhole.

This study was approved by the Institutional Review Board of the Centre Hospitalier Universitaire de Québec – Université Laval (2021-5371) and adheres to the tenets of the Declaration of Helsinki.

2.5.1 Study Cohort

All consecutive patients operated for idiopathic full-thickness MH between 2014 and 2018 at the Centre Hospitalier Universitaire de Québec – Université Laval (Canada) were identified. All patients were operated by one of five vitreoretinal surgeons.

Hospital records were retrospectively reviewed to identify the patients with successful MH closure after primary vitrectomy. Only patients with an anatomic MH closure confirmed by HD-OCT B-scan following surgery were included. Data from patients with unclosed MHs was collected to assess our models' ability to predict the visual outcome in those rare cases, but those were not used to train any of the classification models. Hole closure was defined as the absence of neurosensory retinal defect at the central fovea in all postoperative HD-OCT B-scans at 6 months [5]. Exclusion criteria included patients with a follow-up of less than 6 months after the first surgery, history a vitrectomy for any reason and intraoperative use of a silicone oil tamponade or special techniques (e.g. free flap, inverted flap, retinal autografts, etc.). Eyes with stage 1 MH, lamellar MH, MH secondary to other causes (e.g. trauma, AMD, type 2 macular telangiectasia, and retinal detachment), and eyes with ocular comorbidities that could potentially affect VA including high refractive or axial myopia (≥6 diopters of myopia or axial length ≥26 mm) were excluded. In patients with bilateral MH on initial presentation, only the first operated eye was included. Eyes with significant cataract prior to surgery and eyes that developed clinically significant cataract during the 6 months follow-up were excluded.

2.5.2 Dataset Preparation and Feature Collection

We reviewed the records of all eyes operated for MH with a vitrectomy, ILM peeling and gas or air tamponade. The type of tamponade used was at the discretion of the surgeon with C3F8 often used in more complex cases. All patients were advised to position face-down after surgery for 5 to 7 days.

Pre-operative data included age, sex, lens status, myopia, MH duration defined as the duration between the first reference and the time of surgery [14], baseline CVA, and MH

size. MH size was measured as the minimum hole width or the narrowest aperture size in the middle retina, as defined by the Vitreomacular Traction Study Group [15] on initial presentation. MH measurements were performed by the same person (author A.L.) and validated by a retina specialist (author A.D.) with consensus when discordance.

To reduce overfitting and to gain a better understanding of the clinical importance of each input feature, we decided to select the following features as the main clinical factors predicting final CVA according to the previous literature: baseline CVA, MH size, MH duration, and pseudophakic status [2,4,5]. Operative data included surgical technique, type of dye and type of tamponade used. Postoperative data included CVA at 6 months postoperatively. The CVA originally reported on the Snellen scale was converted to logarithm of the minimal angle of resolution (logMAR) [16]. Lens status and HD-OCT B-scans were recorded at baseline and at 6 months postoperatively.

All patients had undergone HD-OCT imaging using Cirrus 5000 HD-OCT (Carl Zeiss Meditec, Jena, Germany) with 30 degrees centered on the fovea. The individual HD-OCT B-scans horizontal and vertical lines were 750 x 500 pixels. Each patient's image data set was exported as a folder of anonymized non-compressed TIFF files. Our dataset did not include images with improper positioning, low signals, or strong motion artifacts causing misalignment and blurring; no images were excluded.

We make our dataset and codebase publicly available to stimulate and ease further research on the topic.

2.5.3 Training and Validation of DL-Based Model

We randomly split the 121 patients of the dataset into training, validation, and test subsets, each respectively containing 83 (69%), 21 (17%), and 17 (14%) patients. As their names indicate, the training set was used to train DL models, the validation to select the best performing model, and the test set to evaluate the performance of the chosen model in comparison with baselines.

We selected the CBR-Tiny [17] DL model for our experiments because it displays competitive performances on medical imaging datasets despite its simplicity. During training, we leveraged the fact that we have two HD-OCT B-scans (i.e. horizontal and vertical lines) for each patient to artificially double our training samples. At inference time, we took the average of the prediction provided by both HD-OCT B-scans associated with each patient. We applied randomized data augmentation, randomly rotating, flipping horizontally, and

adjusting the brightness and contrast of every image in a training batch. All augmented images were then resized to the 224 x 224 pixels range and then normalized using the mean and standard deviation values from the ImageNet dataset [18]. Every vision model was trained using the binary cross-entropy loss with a batch size of 32, using the Adam [19] optimizer with a learning rate of 0.0001 for a maximum of 1000 gradient steps. We tested the model's performance against the validation set every 50 steps and retained the model with the highest validation area under the receiver operating characteristic curve (AUROC). Visualization heatmaps were generated by Gradient-weighted Class Activation Mapping (Grad-CAM). This was done to help understand the areas of interest on the HD-OCT B-scans which were considered by the DL model.

2.5.4 Regression Model

To provide a baseline for comparison of the DL model's performance, we trained a logistic regression model on clinical features. Hyperparameters used for the logistic regression such as the regularization coefficient were selected using 10-fold cross-validation over the training set. Because our logistic model was trained using cross validation, it did not require a held-out validation set like the DL model. Accordingly, we trained the regression model on samples from both the DL training and validation sets, using the held-out test set to assess performance. Specifically, this meant that our logistic regression model was trained on clinical data of the 104 patients of the testing and validation subsets and tested on the same 17 patients as the DL model. As stated above, the retained features for each patient were: baseline CVA, MH size, MH duration, and pseudophakic status. Before being fed to the model, each patient's clinical data was standardized using the mean and standard deviation of each feature computed on the training set.
Our implementation of the regression model used the LogisticRegressionCV model from scikit-learn [20] with Python version 3.8.

2.5.5 Hybrid Model

From the fully trained deep vision model, we extracted the model's logistic prediction for a patient's HD-OCT B-scans and concatenated it to the patient's clinical data. This clinical data augmented with the vision model's predictions were then used to train another logistic regression, yielding an easy-to-implement way to combine HD-OCT B-scans and clinical

data. Hyperparameters for this hybrid model were selected according to the same procedure as our regression model from clinical data only. An overview of this proposed hybrid model can be seen in **Figure 2.1**.

Many techniques exist to handle multimodal data like our images and clinical features. These techniques, usually classified under late, medium, or early fusion [21], represent an increasing usage of DL, with early fusion meaning the whole multimodal data is fed to a neural network and late fusion meaning only the DL model's prediction is kept. We chose late fusion as this preserves the interpretability. Indeed, because the final prediction is provided by logistic regression, one can compute each feature's importance according to the model, including for the DL model prediction. Albeit potentially less performant, late fusion still represents an interesting avenue in healthcare tasks, where interpretation of the model is highly valuable.

2.5.6 Statistical Analysis

After training and testing our hybrid model, we obtained the predictive output of combining each HD-OCT B-scan with the corresponding patient's clinical data. The confusion matrices were used to calculate the overall accuracy of prediction of visual outcome (CVA gain ≥15 letters) at 6 months. AUROC was used to evaluate the reliability of the model in predicting CVA gain. Other outcome measures included F1 scores, accuracy (ACC), sensitivity (SN), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV).

For both regression-based models (i.e. clinical data only and hybrid), we extracted feature importance for each input feature by computing the ratio between the feature's weight and the sum of all model feature weights.

Data for patient baseline characteristics are presented as mean ± standard deviation for continuous variables and as frequencies (percentages) for categorical variables. Statistical analyses were performed using Python (version 3.8.10; Python Software Foundation) with the Numpy library [22]. Statistical significance was set at $\alpha = 0.05$.

2.5.7 Cross-Validation

Due to the small size of our held-out test set, we performed five-fold cross-validation with all three of our proposed models. For the regression model based solely on clinical features, we split the training set into five mutually exclusive groups, using each group as test set and

the four others as training set for a total of five different runs. We repeated this five-fold cross-validation with five different group separations for a total of 25 runs. For the DL model which also required a validation set for model selection, we repeated the process by using each of the four training folds as validation set, for a total of 100 runs of the DL model. For each DL model run, a corresponding hybrid model run was done by using the trained DL model and its corresponding training and testing sets for regression.

2.5.8 Performance assessment on unclosed MH

Although all our models were trained using our dataset that contains closed cases of MH, it is known that some MH cases may remain unclosed after surgery. To assess our model's ability to predict the visual outcome of such unclosed cases, we tested the performance of our trained hybrid models on the 16 unclosed MH cases of our cohort.

2.6 Results

Characteristics of eyes included in the different subsets (i.e. training, validation and held-out test sets) are shown in **Table 2.1**. Among the 121 patients included (242 HD-OCT B-scans), 88 (73%) were women and the mean age was 67 ± 8 years.

Table 2.2 presents the comparison between the two groups (CVA gain ≥15 letters versus <15 letters) in terms of demographic and clinical features. There was no difference in the type of tamponade and dye used between the two groups (p=0.98 and p=0.11, respectively), which ensures comparability of confounding factors. Vitrectomy with sulfur hexafluoride (SF_6) gas tamponade and indocyanine green (ICG) was most commonly performed. Baseline CVA and MH size were statistically different between the two groups, but MH duration and pseudophakic status were not.

Using only logistic regression on clinical features, in the training set, the AUROC was 80.6 with an F1 score of 78.2. On the held-out test set, the AUROC was 80.6 with an F1 score of 79.7. For the DL model, in the training set, relying solely on the HD-OCT B-scans, the AUROC was 77.3 ± 10.3 with an F1 score of 67.1 ± 28.9. On the held-out test set, the AUROC was 72.8 ± 14.6 with an F1 score of 61.5 ± 23.7.

For our hybrid model, in the training set, the AUROC was 84.09 ± 1.58 with an F1 score 78.0 ± 1.7. On the held-out test set, the AUROC was 81.9 ± 5.2 with an F1 score of 80.4 ± 7.7. Performances of the models on the held-out test and using cross-validation are shown in the **Table 2.3**. All reported results consist of 95% confidence intervals (CI) based on 10 independent training runs. Our models do not require a validation set because the best parameters are selected according to 10-fold validation, hence the absence of validation results.

The receiver operating characteristic (ROC) curves of all independent runs are presented for the clinical, OCT-based DL, and hybrid model in **Figure 2.2**. These results indicate that our hybrid model can provide interesting prediction of postoperative visual improvement with discriminative performances, but this is not significantly better than the clinical data-only logistic regression model.

Heatmaps illustrated the most important region for decision making in our OCT-based DL model (**Figure 2.3**). The fovea was identified as the most critical region for prediction of the clinical ground truth, suggesting that general MH morphology is considered by the model.

For both regression-based models (i.e. clinical data only and hybrid), we reported feature importance for both models in **Figure 2.4**. We see that, for both models, the baseline CVA was the most important feature, being assigned 63.0 ± 0.0% of the model's weight for clinical data only and 59.1 ± 6.9% in the hybrid model. Notably, the OCT prediction only contributes moderately to the hybrid model's output, as its importance ratio is 9.6 ± 4.2%.

We also reported in **Table 2.4** the differences in the preoperative and postoperative factors between eyes predicted correctly and incorrectly by the hybrid model. It was more difficult for the hybrid model to predict the accurate visual outcome when the MH size was smaller (180 ± 38 versus 280 ± 103 µm; p=0.01). MH size was higher in the training set compared to the test set (357 ± 171 and 256 ± 101 µm, respectively; p=0.002) which may explain the lower performances due to less examples of small MH in the training of the DL model. The three most difficult cases to predict are shown in **Figure 2.5**.

Table 2.5 shows the performances of our hybrid model when applied to unclosed MH cases in comparison to our held-out test set of closed MH cases. Overall, we noted no significant

performance difference when testing on unclosed MH cases. F1 scores, AUROC, and ACC for the hybrid model tested with closed MH vs unclosed MH: 80.4 ± 7.7, 81.9 ± 5.3, and 78.7 ± 2.9 versus 77.8 ± 1.4, 79.3 ± 3.1, and 79.4 ± 1.9.

2.7 Discussion

In this study, we developed a hybrid model that used DL on preoperative HD-OCT B-scans and logistic regression on clinical features to predict CVA improvement ≥15 ETDRS letters at 6 months in closed MH after a vitrectomy surgery. Despite the limited total number of OCT scans (n=242), both our models based on clinical data and OCT scans had good discriminative performances. Combining both models into a hybrid model using late fusion yielded marginally better performance, but the improvement was not statistically significant when considering 95 % CIs (clinical data only: AUROC of 80.6 and F1 score of 79.7 versus hybrid model: AUROC of 81.9 ± 5.2 and F1 score of 80.4 ± 7.7); conclusions were similar when we used cross-validation. Given the fact that the hybrid model does not attribute much weight to the prediction provided by the HD-OCT scans (i.e. 9.6 ± 4.2%), it appears that clinical data regression and OCT-based DL are correlated. Much of the information provided by the OCT-based DL model is likely already represented in the clinical data only model as MH morphology in baseline CVA, size and duration of the MH. Moreover, we tested our hybrid model on the unclosed MH of our cohort and the results were similar compared to the held-out test with closed MH (**Table 2.5**), which highlights that the visual prediction of our model is able to generalize to MH that failed to close after the surgery. Thus, the closure of the MH may not be a crucial data to obtain when we have preoperative OCT and clinical variables (especially VA). This may be explained by the fact that information extracted from OCT provides information on the closure of the MH (e.g. large MH size makes closure of the hole less likely). In this way, training a model with a MH that has not closed may not be essential.

Our model based on OCT-based DL is a new and promising alternative to clinical data for prediction of outcomes after surgery. This can lead to new applications in ophthalmology in the future. However, our results need to be contextualized. The difficulty of the task is greater than the DL image classification that detects retinal diseases on OCT as MH, where the AUROC is often much higher (e.g. 97.8%) [10]. Our task is difficult even for an experienced

retinal specialist, it is therefore expected that our combined prediction model cannot reach near-perfect accuracy. Other studies used DL technology to predict anatomic outcome after MH surgery [23, 24]. Despite similarities between these two tasks, the task to predict MH status (closed or open) after the vitrectomy seems to be easier. MH closure essentially amounts understanding the shape of the MH, whereas predicting visual outcome also requires understanding how one MH's shape and its restoration impacts the patient's VA. The postoperative integrity of some layers of the retina like the external limiting membrane (ELM) and the ellipsoid zone are correlated with postoperative VA [25]. The DL model must then include the prediction of arrangement and reorganization of these layers to predict the VA gain.

These results are interesting in real-world clinical settings. Prediction of postoperative visual outcomes can allow clinicians to give a more accurate prognosis to patients and help alleviate their anxiety. This could eventually help ophthalmologists make better surgical decisions in patients with a poor visual prognosis. Our model is built on standard surgical methods for primary MHs with no other pathologic disease that could potentially affect VA, but future investigations could help to predict vision in eyes with concomitant other eye diseases, such as diabetic macular edema. Although the difficulty of this task is greater, advanced work in DL in connection with this pathology could be favorable [11].

OCT imaging is a useful way of measuring various aspects of MH morphology with high precision and reproducibility [26]. Some OCT-defined parameters have been used as prognostic factors of visual outcomes in closed MH after surgery [6-8]. However, these OCT-defined parameters were evaluated individually in previous studies. The accuracy and applicability of these prediction algorithms using single factors are limited, whereas visual outcomes after MH surgery are influenced by multiple factors. Clinical data are also crucial to better understand VA improvement. Three characteristics are important for prediction and included in our model: preoperative VA, MH duration, and MH size [2,4,5]. Eyes with better baseline VA generally obtain better postoperative VA, whereas eyes starting with worse VA have more potential VA gain [27-29]. Moreover, MHs of shorter durations are associated with better visual outcomes as the integrity of the macular structure and ELM are better preserved [25]. Furthermore, an inverse correlation between MH size and postoperative VA is well recognized, with larger MH typically associated with worse visual outcomes [30,31]. Lens status was also included (i.e. phakic or pseudophakic) to limit the effect of progressive

cataract development in a patient with a phakic lens on postoperative VA. In our study, we propose a straightforward way to integrate DL on OCT images and relevant clinical data to make accurate predictions of postoperative visual improvement.

Concurrently to our work, Obata et al. also investigated the task of predicting VA after MH surgery, finding that a DL model on OCT scans performed better than logistic regression from clinical data [32]. Although closely related to our approach, their work differed in the prediction task given to the model. Indeed, whereas our approach aimed to provide binary classification (whether the VA will increase by 15 ETDRS at 6 months or not), their task was a multiclass classification (whether a patient's VA will be within 4 different ranges after surgery). The latter was an intuitively harder task and was probably the reason behind their lower performances (precision of 46% for the DL model) compared with ours. Moreover, they compared their DL model to a multiple linear regression model in which clinical data included preoperative VA, MH size, and age with no inclusion of pseudophakic status. In our study, 15.2 ± 1.6% of the model's weight of the hybrid model was related to pseudophakic status. This is likely less relevant in Obata et al.'s work given that they performed phacovitrectomy in 99% (236/238) of patients with phakic lenses.

In future works, our approach can probably benefit from using transfer learning. In transfer learning, a DL model is initially trained on an auxiliary task usually related to the task at hand. Using the pretrained model's weights as a starting point, the fully trained model's performance can then be improved with a smaller sample size for the target task. This is of particular interest in the medical field where imaging data is more difficult to obtain in large quantities [33, 34]. Another interesting research direction would be to consider other fusion schemes than late fusion [21] for the hybrid model. Indeed, whereas late fusion enjoys the desirable property of preserving interpretability, it still represents a very limited source of information sharing between the clinical data and the OCT models. Other approaches fall into the early and medium fusion categories [21], potentially increasing the hybrid model's performance at the cost of losing interpretability. Recently, one such early fusion model for prediction of the anatomical outcome of MH surgery was proposed by Xiao et al. [35] who found that a hybrid model had better performance than a model based exclusively on OCT scans and clinical data (AUROC of 90.4, 80.4, and 79.7, respectively). We hypothesize that significant gain in performance found when compared to our work is attributable to the easier nature of the anatomic task as well as their hybrid model's increased capacity. To this end,

we hope that making our dataset and codebase publicly available will enable other researchers to further progress on the proposed task, by testing the above proposed methods or through their own alternatives.

This study has limitations. As seen in **Table 2.1**, the DL model trained on MH with larger diameters than in the test set (p=0.02) and ended up making more mistakes on smaller MH sizes, as seen in **Table 2.4**. This discrepancy in the MH sizes between sets was an artifact of our random sampling procedure to separate the train and test patients. In our procedure, we randomly assigned the MHs in the groups, ensuring the visual outcomes in both sets were as similar as possible while attempting to also do the same for clinical features. Considering the high variance in patients across all features and the small size of the test set (17 patients), one can hardly expect to have feature distributions that are as similar as the two sets we used. Moreover, it is well known that baseline CVA is the most important clinical predictor (hybrid model weight of baseline CVA: 59.1±6.9%), and this information was separated adequately between train and test sets [4]. We considered our random split to be as accurate as possible given our limited number of patients. It is to be expected that the model will be more accurate on patients that are similar to what it was trained on, so the lower occurrence of large MH sizes in the training set probably explains why the model's performance worsens on smaller MH sizes. One way to possibly alleviate this performance discrepancy would be to use stratification based on the MH size attribute. We chose not to use stratification because it would have significantly reduced the amount of data available to train on, which was already a bottleneck for our DL model.

Moreover, cataract surgery can have a significant impact on the results, but we took all the measures to limit its effect. Eyes with significant cataract prior to surgery and eyes that developed clinically significant cataract during the 6 months of follow-up were excluded. Moreover, we selected the prediction at 6 months to minimize the development of cataract in phakic eyes. In addition, few eyes had phacovitrectomy (1 eye) and no patients had a cataract surgery during the follow-up.

Our model had a relatively small sample size, issued from a single center. Perspectives for external validation are underway. Currently, our hospital center does not have new data to assess external validity and no public dataset contains OCT with the necessary clinical information as CVA [36]. That said, this is a preliminary study to evaluate the feasibility of

predicting postoperative CVA improvement with DL methods. Further studies are also needed to determine the mechanisms guiding model prediction.

In conclusion, despite the limited total number of OCT scans, both models from clinical data and OCT scans had good discriminative performances. Combining both models into a hybrid model yielded marginally better performance, although the improvement was not statistically significant. Our models allow prediction of visual improvement after successful MH closure surgery. These models could eventually help ophthalmologists for surgical planning of MH surgery and better care for patients with tailored visual prognoses.

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2.9 References

[1] Lachance A, You E, Garneau J, et al. Revision Surgery for Idiopathic Macular Hole after Failed Primary Vitrectomy. *J Ophthalmol*. 2021:8832538. doi: 10.1155/2021/8832538.

[2] Fallico M, Jackson TL, Chronopoulos A, et al. Factors predicting normal visual acuity following anatomically successful macular hole surgery. *Acta Ophthalmol*. 2021;99(3):e324-e329. doi: 10.1111/aos.14575.

[3] Yek JTO, Hunyor AP, Campbell WG, et al. Outcomes of eyes with failed primary surgery for idiopathic macular hole. *Ophthalmol Retina*. 2018; 2(8):757–764. doi: 10.1016/j.oret.2017.10.012.

[4] Essex RW, Hunyor AP, Moreno-Betancur M, et al. Australian and New Zealand Society of Retinal Specialists Macular Hole Study Group. The visual outcomes of macular hole surgery: a registry-based study by the Australian and New Zealand society of retinal specialists. *Ophthalmol Retina*. 2018;2(11):1143–1151. doi: 10.1016/j.oret.2018.04.022.

[5]. 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. doi: 10.1038/s41433-020-0844-x.

[6] Murphy DC, Nasrulloh AV, Lendrem C, et al. Predicting Postoperative Vision for Macular Hole with Automated Image Analysis. *Ophthalmol Retina*. 2020;4(12):1211-1213. doi: 10.1016/j.oret.2020.06.005.

[7] Geng XY, Wu HQ, Jiang JH, et al. Area and volume ratios for prediction of visual outcome in idiopathic macular hole. *Int J Ophthalmol*. 2017;10(8):1255-1260. doi: 10.18240/ijo.2017.08.12.

[8] Xu D, Yuan A, Kaiser PK, et al. A novel segmentation algorithm for volumetric analysis of macular hole boundaries identified with optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54(1):163-9. doi: 10.1167/iovs.12-10246.

[9] Xu J, Ishikawa H, Wollstein G, Schuman JS. 3D OCT eye movement correction based on particle filtering. *Annu Int Conf IEEE Eng Med Biol Soc*. 2010; 2010:53-6. doi: 10.1109/IEMBS.2010.5626302.

[10] Lu W, Tong Y, Yu Y, et al. Deep Learning-Based Automated Classification of Multi-Categorical Abnormalities From Optical Coherence Tomography Images. *Transl Vis Sci Technol*. 2018;7(6):41. doi: 10.1167/tvst.7.6.41.

[11] Li F, Chen H, Liu Z, et al. Deep learning-based automated detection of retinal diseases using optical coherence tomography images. *Biomed Opt Express*. 2019;10(12):6204-26. doi: 10.1364/BOE.10.006204.

[12] Liu B, Zhang B, Hu Y, et al. Automatic prediction of treatment outcomes in patients with diabetic macular edema using ensemble machine learning. *Ann Transl Med*. 2021;9(1):43. doi: 10.21037/atm-20-1431.

[13] Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci*. 2009;50(8):3629-35. doi: 10.1167/iovs.08-3225.

[14] Lumi X, Mahnic M, Petrovski BE, Petrovski G. Outcomes of Vitrectomy for Long-Duration Macular Hole. *J Clin Med*. 2020;9(2):444. doi: 10.3390/jcm9020444.

[15] 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. doi: 10.1016/j.ophtha.2013.07.042.

[16] Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *Retina*. 2010;30(7):1046-50. doi: 10.1097/IAE.0b013e3181d87e04.

[17] Raghu M, Zhang C, Kleinberg J, Bengio S. Transfusion: Understanding transfer learning for medical imaging. *arXiv preprint*. 2019;arXiv:1902.07208.

[18] Deng J, Dong W, Socher Z, Li LJ, Li K, Fei-Fei L. Imagenet: A large-scale hierarchical image database. *In 2009 IEEE conference on computer vision and pattern recognition*. 2009:248–255.

[19] Diederik P Kingma and Jimmy Ba. Adam: A method for stochastic optimization. *arXiv preprint*. 2014;arXiv:1412.6980.

[20] Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research*. 2011(12): 2825-2830.

[21] Huang SC, Pareek A, Seyyedi S, Banerjee I, Lungren MP. Fusion of medical imaging and electronic health records using deep learning: a systematic review and implementation guidelines. *NPJ Digit Med*. 2020;3:136. doi: 10.1038/s41746-020-00341-z.

[22] Harris CR, Millman KJ, van der Walt SJ, et al. Array programming with NumPy. *Nature.* 2020;585(7825):357-362. doi: 10.1038/s41586-020-2649-2.

[23] Hu Y, Xiao Y, Quan W, et al. A multi-center study of prediction of macular hole status after vitrectomy and internal limiting membrane peeling by a deep learning model. *Ann Transl Med*. 2021;9(1):51. doi: 10.21037/atm-20-1789.

[24] Xiao Y, Hu Y, Quan W, et al. Machine learning-based prediction of anatomical outcome after idiopathic macular hole surgery. *Ann Transl Med*. 2021;9(10):830. doi: 10.21037/atm-20-8065.

[25] Kaźmierczak K, Stafiej J, Stachura J, Żuchowski P, Malukiewicz G. Long-Term Anatomic and Functional Outcomes after Macular Hole Surgery. *J Ophthalmol*. 2018:3082194. doi: 10.1155/2018/3082194.

[26] Ruiz-Moreno JM, Staicu C, Piñero DP, et al. Optical coherence tomography predictive factors for macular hole surgery outcome. *Br J Ophthalmol*. 2008;92(5):640-4. doi: 10.1136/bjo.2007.136176.

[27] Scott RA, Ezra E, West JF, Gregor ZJ. Visual and anatomical results of surgery for long standing macular holes. *Br J Ophthalmol*. 2000;84(2):150-153. doi: 10.1136/bjo.84.2.150.

[28] Jaycock PD, Bunce C, Xing W, et al. Outcomes of macular hole surgery: implications for surgical management and clinical governance. *Eye (Lond)*. 2005;19(8):879-84. doi: 10.1038/sj.eye.6701679.

[29] Gupta B, Laidlaw DA, Williamson TH, Shah SP, Wong R, Wren S. Predicting visual success in macular hole surgery. *Br J Ophthalmol*. 2009;93(11):1488-91. doi: 10.1136/bjo.2008.153189.

[30] Ezra E, Gregor ZJ, Morfields Macular Hole Study Group Report No. 1. 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*. 2004;122(2):224-36. doi: 10.1001/archopht.122.2.224.

[31] 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):390-3. doi: 10.1136/bjo.86.4.390.

[32] Obata S, Ichiyama Y, Kakinoki M, et al. Prediction of postoperative visual acuity after vitrectomy for macular hole using deep learning-based artificial intelligence. *Graefes Arch Clin Exp Ophthalmol*. 2021. doi: 10.1007/s00417-021-05427-2.

[33] Xie Y, Richmond D. Pre-training on grayscale imagenet improves medical image classification. *In Proceedings of the European Conference on Computer Vision (ECCV) Workshops*. 2018:0-0.

[34] Rajpurkar P, Park A, Irvin J, et al. AppendiXNet: Deep Learning for Diagnosis of Appendicitis from A Small Dataset of CT Exams Using Video Pretraining. *Sci Rep*. 2020;10(1):3958. doi: 10.1038/s41598-020-61055-6.

[35] Xiao Y, Hu Y, Quan W, et al. Development and validation of a deep learning system to classify aetiology and predict anatomical outcomes of macular hole. *Br J Ophthalmol*. 2021: 318844. doi: 10.1136/bjophthalmol-2021-318844.

[36] Khan SM, Liu X, Nath S, et al. A global review of publicly available datasets for ophthalmological imaging: barriers to access, usability, and generalisability. *Lancet Digit Health*. 2021;3(1):e51-e66. doi: 10.1016/S2589-7500(20)30240-5.

2.10 Tables

Table 2.1. Characteristics for Patients of the Different Splits in the Data Set

	Training Set *(n*=104*)*	**Test Set** *(n*=17*)*	**Total Set** *(n*=121*)*	***P* Value**
Age, years ± SD	66 ± 8	69 ± 7	67 ± 8	0.12
Sex				0.84
Female, n (%)	76 (73)	12 (71)	88 (73)	
Male, n (%)	28 (27)	5 (29)	33 (27)	
Baseline CVA, letters ± SD	50 ± 15	51 ± 18	50 ± 16	0.83
MH size, μm ± SD	357 ± 171	256 ± 101	343 ± 167	0.002
MH duration, weeks ± SD	11 ± 10	10 ± 5	11 ± 9	0.53
Pseudophakic, n (%)	18 (17)	4 (24)	22 (18)	0.54
Phacovitrectomy, n (%)	1 (1)	0 (0)	1 (1)	0.68
CVA at 6 months, letters ± SD	66 ± 12	66 ± 11	66 ± 12	1.00
CVA gain ≥15 letters, n (%)	52 (50)	8 (47)	60 (50)	0.83
Stage of MH				0.81
Stage 2, n (%)	16 (15)	3 (18)	19 (16)	
Stage 3, n (%)	64 (62)	10 (59)	74 (61)	
Stage 4, n (%)	24 (23)	4 (24)	28 (23)	

MH, macular hole; CVA, corrected visual acuity; SD, standard deviation.

Table 2.2. Comparison Between the Two Groups (CVA gain ≥15 letters versus <15 letters) in Terms of Demographic and Clinical Features

Features	CVA gain ≥15 Letters (*n*=60)	CVA gain <15 Letters (*n*=61)	Total Set (*n*=121)	*P* Value
Age, years ± SD	67 ± 15	67 ± 14	67 ± 15	1.00
Sex				0.17
Female, n (%)	47 (78)	41 (67)	88 (73)	
Male, n (%)	13 (22)	20 (33)	33 (27)	
Baseline CVA, letters ± SD	42 ± 15	59 ± 10	50 ± 16	<0.0001
MH size, µm ± SD	394 ± 183	293 ± 131	343 ± 167	0.0008
MH duration, weeks ± SD	11 ± 12	10 ± 7	10 ± 10	0.58
Pseudophakic, n (%)	15 (25)	7 (12)	22 (18)	0.05
Phacovitrectomy, n (%)	0 (0)	1 (2)	1 (2)	0.32
CVA at 6 months, letters ± SD	70 ± 9	62 ± 12	66 ± 12	<0.0001
Stage of MH				0.53
Stage 2, n (%)	10 (17)	9 (15)	19 (16)	
Stage 3, n (%)	35 (58)	39 (64)	74 (61)	
Stage 4, n (%)	15 (25)	13 (21)	28 (23)	
Surgery procedure				
Vitrectomy; ILM peeling, n (%)	60 (100)	61 (100)	121 (100)	0.99
Tamponade used				0.98
SF_6, n (%)	53 (88)	54 (89)	107 (88)	
C_3F_8, n (%)	7 (12)	7 (12)	14 (12)	
Dye used				0.11
ICG, n (%)	43 (72)	51 (84)	94 (78)	
TB, n (%)	17 (28)	10 (16)	27 (22)	

MH, macular hole; ILM, internal limiting membrane; CVA, corrected visual acuity; ICG, indocyanine green; TB, trypan blue; SD, standard deviation.

Table 2.3. Performances of the Models on the Held-Out Test and Using Cross-Validation

Models	F1 scores	AUROC	ACC	SP	SN	PPV	NPV
Clinical							
Train	**78.2**	79.3	76.0	**88.5**	**71.7**	**80.0**	72.9
Test	79.7	80.6	**80.2**	89.7	72.3	**80.0**	**81.8**
OCT-based DL							
Train	67.1 ± 28.9	77.3 ± 10.3	69.8 ± 3.6	76.9 ± 25.2	65.4 ± 15.6	57.6 ± 14.4	**81.4** ± 9.0
Test	61.5 ± 23.7	72.8 ± 14.6	63.9 ± 13.2	70.8 ± 30.2	60.2 ± 17.9	60.2 ± 15.4	76.9 ± 15.4
Hybrid							
Train	78.0 ± 1.7	**84.1** ± 1.6	**76.9** ± 4.2	79.0 ± 16.8	**76.4** ± 26.8	74.2 ± 9.4	78.8 ± 7.6
Test	**80.4** ± 7.7	**81.9** ± 5.2	78.7 ± 2.9	**91.3** ± 15.9	67.8 ± 26.9	77.4 ± 4.3	80.8 ± 6.7
Clinical cross-validation							
Train	**77.0** ± 2.1	**82.4** ± 2.7	**76.5** ± 5.3	84.7 ± 9.9	64.2 ± 19.9	72.6 ± 9.5	**83.2** ± 6.9
Test	**81.0** ± 7.1	**81.5** ± 11.2	**80.3** ± 10.8	**97.2** ± 5.0	55.4 ± 23.2	70.4 ± 11.0	86.7 ± 5.9
OCT-based DL cross-validation							
Train	74.0 ± 3.7	75.3 ± 6.9	73.5 ± 7.3	**85.2** ± 8.5	53.8 ± 21.5	66.8 ± 9.0	79.5 ± 7.3
Test	76.3 ± 6.8	74.8 ± 11.1	74.9 ± 10.3	87.3 ± 11.2	57.2 ± 25.8	70.3 ± 13.5	81.3 ± 14.6
Hybrid cross-validation							
Train	76.8 ± 2.6	82.2 ± 3.2	76.4 ± 5.6	80.6 ± 9.8	**70.1** ± 20.0	**75.7** ± 10.5	80.0 ± 6.0
Test	80.1 ± 7.6	81.7 ± 10.6	79.3 ± 10.7	92.4 ± 9.3	**60.2** ± 23.6	**72.3** ± 12.6	**90.6** ± 10.3

DL, deep learning; AUROC, area under the receiver operating characteristic curve; ACC, accuracy; SP, specificity; SN, Sensitivity; PPV, positive predictive value; NPV, negative predictive value; Best means are highlighted.

Table 2.4. The Differences in the Pre-operative and Postoperative Factors Between Eyes Predicted Correctly and Incorrectly by the Hybrid Model. MH size is smaller in the eyes predicted incorrectly

	Eyes Predicted Correctly *(n=13)*	**Eyes Predicted Incorrectly** *(n=4)*	***P* Value**
Age, years ± SD	70 ± 7	66 ± 3	0.13
Sex			0.83
Female, n (%)	9 (69)	3 (75)	
Male, n (%)	4 (31)	1 (25)	
Baseline CVA, letters ± SD	51 ± 19	49 ± 11	0.80
MH size, μm ± SD	280 ± 103	180 ± 38	0.01
MH duration, weeks ± SD	9 ± 7	9 ± 4	1.00
Pseudophakic, n (%)	2 (15)	2 (50)	0.15
Phacovitrectomy, n (%)	0 (0)	0 (0)	1.00
CVA at 6 months, letters ± SD	67 ± 7	66 ± 3	0.69
CVA gain ≥15 letters, n (%)	6 (46)	2 (50)	0.90
Stage of MH			0.05
Stage 2, n (%)	1 (8)	2 (50)	
Stage 3, n (%)	9 (69)	1 (25)	
Stage 4, n (%)	3 (23)	1 (25)	

MH, macular hole; CVA, corrected visual acuity; SD, Standard deviation.

Table 2.5. Performances of the Hybrid Model on the Held-Out Test on Unclosed Versus Closed Macular Holes After the First Vitrectomy. The performances are similar which indicates that our hybrid model well generalized to MH that failed to close after the first vitrectomy

Hybrid model	F1 scores	AUROC	ACC	SP	SN	PPV	NPV
Test set (closed MH)	80.4 ± 7.7	81.9 ± 5.2	78.7 ± 2.9	91.3 ± 15.9	67.8 ± 26.9	77.4 ± 4.3	80.8 ± 6.7
Unclosed MH set	77.8 ± 1.4	79.3 ± 3.1	79.4 ± 1.9	100.0 ± 0.0	72.7 ± 2.0	69.7 ± 1.0	100.0 ± 0.0

DL, deep learning; AUROC, area under the receiver operating characteristic curve; ACC, accuracy; SP, specificity; SN, sensibility; PPV, positive predictive value; NPV, negative predictive value.

2.11 Figures

Figure 2.1. Overview of our proposed hybrid model. *(Top)* Illustration of the extraction of the OCT-based prediction from the trained DL model. *(Bottom)* Flow-chart representing the combination of clinical data and OCT-based data to predict the clinical ground truth.

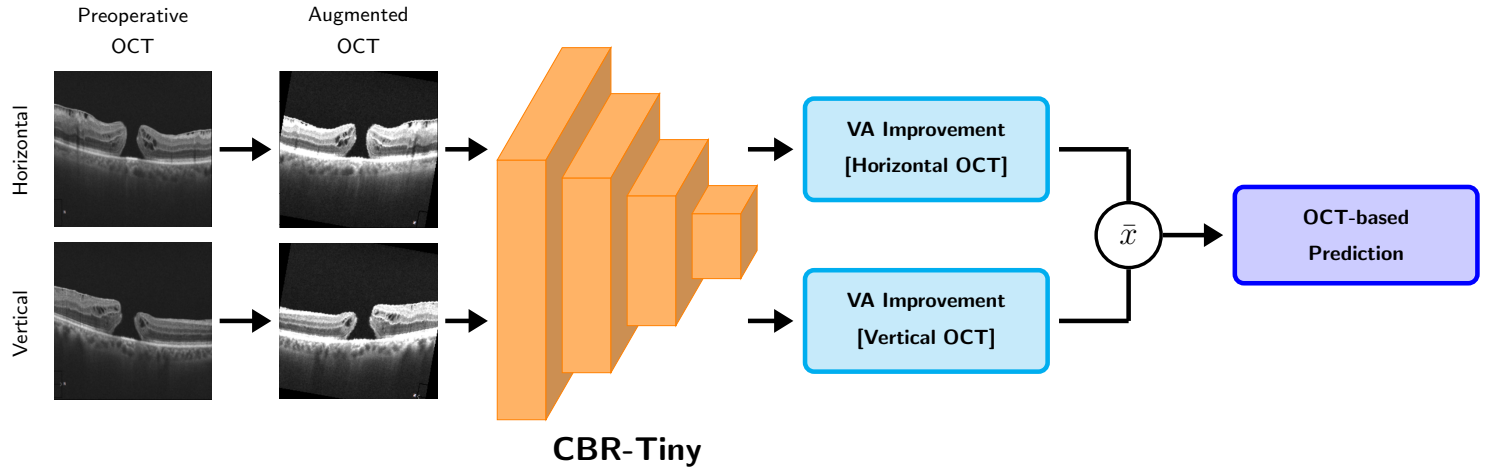


Figure 2.2. The receiver operating characteristic (ROC) curves on the cross-validation and held-out test set for all three models. We report the mean value and a 95 % CI computed from 100 independent runs for the DL and hybrid models and 25 runs for the clinical data regression model. For each independent run, we plotted the corresponding ROC curve in a different color.

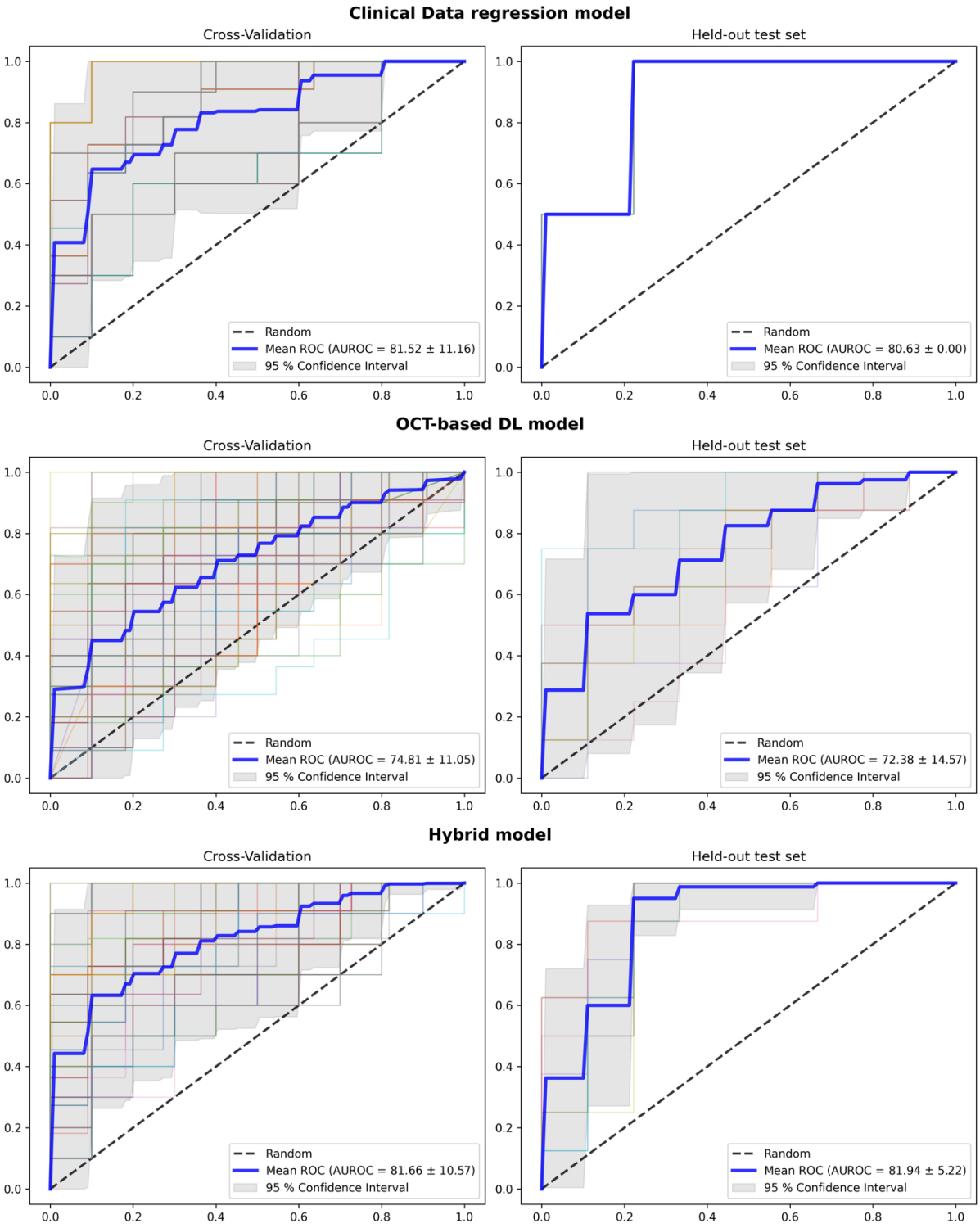
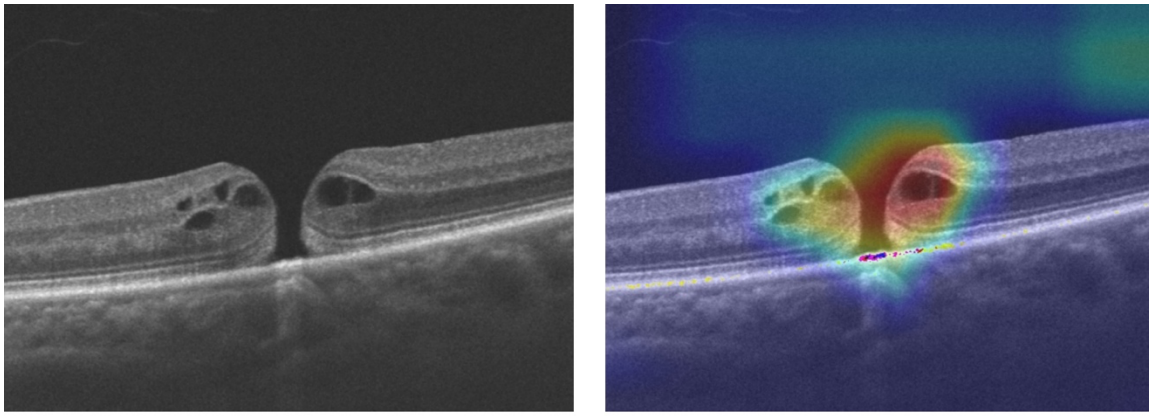


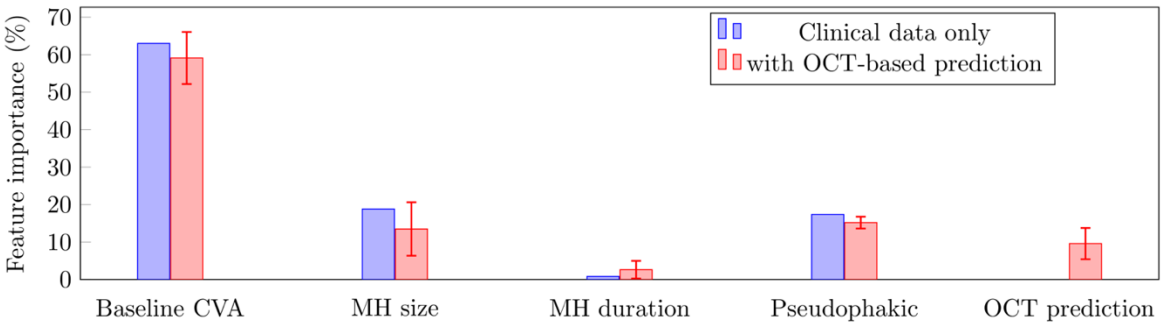
Figure 2.3. Visualization heatmap for prediction of the clinical ground truth. The heatmap was generated by Gradient-weighted Class Activation Mapping (Grad-CAM). The heatmap highlights the pathological area (fovea) as being most important for accurate prediction of CVA improvement after surgery in HD-OCT B-scans.



(A) (B)

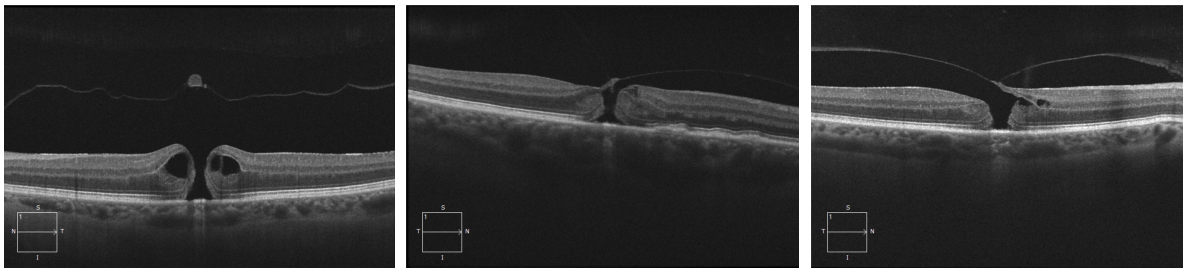
(A) Original image. (B) Grad-CAM.

Figure 2.4. Feature importance ratio (%) attributed by the regression models with and without the addition of the OCT-based prediction. For each feature, we reported the average and standard deviation computed from 10 independent runs. The standard deviation is 0 for all features when using only clinical data because the clinical features are always strictly the same in this case.



CVA, corrected visual acuity.

Figure 2.5. Horizontal HD-OCT of the three most difficult cases to predict on the held-out test with the hybrid model.



Hole size: 144 μm | Hole size: 152 μm | Hole size: 240 μm

Chapitre 3 - Revision Surgery for Idiopathic Macular Hole after Failed Primary Vitrectomy

3.1 Résumé

OBJECTIF: Étudier les résultats anatomiques et fonctionnels de la chirurgie de révision après l'échec de la chirurgie primaire pour un trou maculaire idiopathique (TM).

MÉTHODES: Tous les patients atteints de TM ont été identifiés à partir d'une cohorte de patients opérés entre 2014 et 2018 au CHU de Québec-Université Laval (Québec). Les caractéristiques cliniques et anatomiques des patients atteints de TM non fermés après une chirurgie primaire ont été recueillies rétrospectivement. L'issue principale mesurée était le taux de non-fermeture des TM après l'intervention chirurgicale de reprise. L'issue secondaire consistait en la meilleure acuité visuelle corrigée (MAVC) avec l'échelle ETDRS ainsi que la taille des TM avec une chirurgie de révision en préopératoire, à 3 mois et 12 mois après la chirurgie de révision.

RÉSULTATS: Dans notre cohorte de 1085 yeux, 926 yeux répondaient aux critères d'inclusion et ont été analysés dans l'étude. Nous avons identifié 22 yeux avec échec de chirurgie primaire (2.4%), dont 20 ont subi une chirurgie de révision. Nous n'avions pas de TM bilatéral dans ces 22 yeux. Le taux de non-fermeture des TM après la chirurgie de révision était de 15%. La MAVC finale moyenne pour les TM fermés après la chirurgie de révision était de 55 ± 19 lettres. Par rapport à la présentation initiale, le changement moyen de l'acuité visuelle (AV) pour les TM fermés était de +4 ± 31 lettres et +16 ± 17 lettres à 3 et 12 mois après la chirurgie de révision, respectivement. Lors de la présentation initiale, les patients dont la chirurgie primaire a échoué avaient une taille de base de leur TM de 665 ± 226 µm. La taille moyenne des TM après échec de la chirurgie primaire était de 607 ± 162 µm et 546 ± 156 µm pour les trois TM non fermés un mois après la chirurgie de révision.

CONCLUSION: Le taux de réussite de la chirurgie de révision dans les yeux avec TM non fermés était de 85%. Après une chirurgie de révision réussie, les yeux ont montré une amélioration de l'AV et de la fermeture du TM.

3.2 Abstract

PURPOSE: To investigate the anatomical and functional outcomes of revision surgery after failed primary surgery for idiopathic macular hole (MH).

METHODS: All consecutive patients with MH were identified from a cohort of patients operated between 2014 and 2018 at the CHU de Québec-Université Laval (Québec). The clinical and anatomical features of patients with unclosed MH after primary surgery were retrospectively collected. Our primary outcome was MH nonclosure rate after revision surgery. Our secondary outcomes were best-corrected visual acuity (BCVA) with ETDRS scale and MH size of eyes with revision surgery preoperatively and at 3 and 12 months after revision surgery.

RESULTS: In our cohort of 1085 eyes, 926 eyes met inclusion criteria and were analyzed in the study. We identified 22 eyes with failed primary surgery (2.4%), of which 20 underwent revision surgery. We had no bilateral MH in these 22 eyes. The nonclosure rate of MH after revision surgery was 15%. The mean final BCVA for closed MH after revision surgery was 55 ± 19 letters. Compared to the initial presentation, the mean change in visual acuity (VA) for closed MH was +4 ± 31 letters and +16 ± 17 letters at 3 and 12 months after the revision surgery, respectively. At initial presentation, patients with failed primary surgery had a baseline MH size of 665 ± 226 µm. The mean MH size after failed primary surgery was 607 ± 162 µm and 546 ± 156 µm for the three unclosed MHs one month after revision surgery.

CONCLUSION: The success rate of revision surgery in eyes with unclosed MH is 85%. After successful revision surgery, eyes demonstrated an improvement in VA and closure of the MH.

Key words: Internal limiting membrane, FLAP technique, transplantation, persistent

3.3 Page titre

Revision Surgery for Idiopathic Macular Hole after Failed Primary Vitrectomy

Abbreviated title: Outcomes of Revision Macular Hole Surgery

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3.4 Introduction

A full-thickness macular hole (MH) is a defect of all the neurosensory retinal layers involving the fovea, resulting in a marked reduction in visual acuity (VA) and metamorphopsia. Most MHs are idiopathic in etiology although MH may also be secondary to other causes such as trauma, high myopia, age-related macular degeneration (AMD), retinal detachment, and type 2 macular telangiectasia [1]. Idiopathic full-thickness MHs result from changes at the vitreomacular interface. The mechanism is not yet fully understood, but perifoveal vitreous traction related to the process of posterior vitreous detachment (PVD) has been proposed as the primary mechanism [2]. The mainstay of MH treatment is a pars plana vitrectomy with endotamponade using SF_6, C_3F_8, air, or silicone oil [1]. The reported rate of successful surgical closure of idiopathic MH varies between 78% and 96% [3]. Management options after a failed primary vitrectomy for idiopathic MH include observation, tamponade exchange, and revision vitrectomy with different approaches to the internal limiting membrane (ILM). Other surgical techniques that have been employed for challenging cases include retinal autografts, amniotic membrane grafts, and induced retinal detachment at the macula. However, limited data exist on the best approach for unclosed idiopathic MH as well as their outcomes following reoperation. A large variation in surgical techniques and small study sizes may contribute to the difficulty of evaluating optimal management of MH refractory to primary vitrectomy [4]. Therefore, the aim of this study is to evaluate the anatomical and functional outcomes of revision surgery in eyes with idiopathic full-thickness MH that failed to close after primary surgery.

3.5 Methods

All consecutive patients that were operated for full-thickness MH surgery between 2014 and 2018 at the Centre Hospitalier Universitaire (CHU) de Québec-Université Laval, Québec, were identified. Patient records were systematically reviewed to identify patients with nonclosure in the postoperative follow-up period. Patients with a follow-up of less than four weeks after the first surgery were excluded. Only patients with idiopathic full-thickness MH were included in the analysis. Patients with stage 1 MH, lamellar MH, recurrent MH after an

initially successful primary surgery, and MH secondary to other causes (i.e., trauma, AMD, type 2 macular telangiectasia, and retinal detachment) were also excluded.

The medical records of all patients included were systematically reviewed, and the data were recorded in an electronic data collection form. Preoperative data collected included age, sex, lens status, myopia, duration of symptoms prior to the primary surgery, and baseline VA and MH size on initial presentation. Operative data included surgical technique, method of tamponade, and internal limiting membrane peeling. Postoperative data included VA and MH size at 3 and 12 months postoperatively. Lens status was recorded at each visit. The VA originally reported on the Snellen scale was converted to ETDRS letters. All optical coherence tomography (OCT) scans were performed using the CIRRUS HD-OCT 5000 machine (Carl Zeiss Meditec, Jena, Germany). The MH size was determined as the minimum width of the MH at the narrowest point in the middle retina, as defined by the Vitreomacular Traction Study Group [5]. We also evaluated the time elapsed between initial symptoms and primary MH surgery and time to reoperation after the first unsuccessful surgery.

Our primary outcome was the rate of MH nonclosure after revision surgery. Our secondary outcomes included best-corrected visual acuity (BCVA) and MH size in eyes with failed primary surgery before and at 3 and 12 months after the revision surgery. MH closure was evaluated at 6 to 8 weeks of follow-up for patients with gas tamponade and after the removal of silicone oil for patients with silicone oil tamponade. Descriptive statistics using SPSS software were performed. The study was approved by the Research Ethics Committee of the Centre Hospitalier Universitaire (CHU) de Québec-Université Laval (2021-5371).

3.6 Results

During the study period, 1085 eyes were operated for MH. Of these, 159 eyes were excluded as per the exclusion criteria outlined in our methodology. Out of 926 eyes analyzed, 22 eyes had a failed primary surgery. Twenty eyes subsequently underwent revision surgery with successful closure in 17 of the 20 eyes (**Figure 3.1**). Therefore, the nonclosure rates of MH after primary surgery and revision surgery were 2.4% and 15%, respectively. Alternatively, the closure rates were 97.6% and 85% after primary and revision surgery, respectively.

The clinical and demographic characteristics of patients with unclosed MH upon initial presentation are shown in **Table 3.1**. The mean age of patients undergoing revision surgery was 73 ± 6 years and 68 ± 13 years for patients who did not attempt revision surgery. Among patients undergoing revision surgery, 7 (35%) patients were men and 13 (65%) were women. The two patients who did not attempt revision surgery were men. Eyes that underwent successful revision surgery had a shorter duration of symptoms at first presentation compared to those with an unsuccessful revision surgery (24 ± 21 (n = 17) vs. 46 ± 33 weeks (n = 3)). Eyes that underwent successful revision surgery had a smaller baseline MH size before the first surgery compared to those with an unsuccessful revision surgery (630 ± 237 μm (n = 17) vs. 781 ± 174 μm (n = 3)). The baseline MH size in eyes that did not attempt revision surgery was larger (790 ± 170 μm (n = 2)). Eyes that underwent successful revision surgery had a smaller hole size after the first failed surgery compared to those with an unsuccessful revision surgery (559 ± 117 (n = 17) vs. 859 ± 167 μm (n = 3)). The VA before the first surgery was 33 ± 27 letters (n = 17) for those with successful revision surgery, 33 ± 23 letters (n = 3) for those with failed revision surgery, and 41 ± 0 letters (n = 2) for those who did not attempt revision surgery.

Details of the revision surgery procedure are shown in **Table 3.2**. In successful revision surgery, techniques employed were 70% (12/17) vitrectomy with ILM peeling (peripheral extension of outer borders of ILM peeling (n = 8) or removal of a remnant ILM at foveal borders (n = 4)), 12% (2/17) changing tamponade with no complementary peeling, 12% (2/17) inverted flap technique (done with a remnant of ILM flap at the foveal border), and 6% (1/17) ILM transfer (free flap). For unsuccessful revision procedures, the surgery performed was vitrectomy with peeling of the remnant ILM (peripheral extension of outer borders of ILM peeling) (n = 1), changing tamponade with no complementary peeling (n = 1), and ILM transfer (free flap) (n = 1). Fifteen of 17 eyes (88%) with successful revision surgery and all eyes (n = 3) in unsuccessful revision surgery received C3F8 gas. Each patient was advised to position face-down after surgery for at least one week.

The VA after revision surgery is shown in **Table 3.3**. In eyes with failed primary surgery, the VA decreased slightly immediately after the first surgery (33 ± 26 letters to 21 ± 36 letters (n = 20)). At 3 months following revision surgery (n = 16), the mean VA was improved to 35 ± 32 letters with a mean change in VA compared to VA before the first surgery of +3 ± 33

letters. VA increased greater than or equal to 0 letters in n = 12 eyes and greater than or equal to 15 letters in n = 5 eyes. At 12 months following revision surgery (n = 6), the mean VA was 55 ± 19 letters, and the mean change in VA compared to VA before the first surgery was +16 ± 17 letters. VA increased greater than or equal to 0 letters in n = 5 eyes and greater than or equal to 15 letters in n = 3 eyes.

The evolution of the MH size after the revision surgery is shown in **Table 3.4**. Eyes with failed revision surgery (n = 3) had a width of 546 ± 156 (n = 3) and 849 ± 0 (n = 1) μm at 1 and 3 months, respectively, after revision surgery. The data at 12 months was missing. In our study, 73% of eyes were phakic before the first surgery and 32% remained phakic 12 months after revision surgery.

3.7 Discussion

Despite the relatively high success rate following primary surgery, the persistence of MH remains a surgical challenge, affecting 8–44% of all operated MHs [6]. The optimal approach to failure-to-close cases, as well as the added value of reoperating, is still up for debate. In our study, 91% of all failed primary closure of MH underwent revision surgery. These patients typically had a worse preoperative acuity (21 ± 36 vs. 41 ± 0 letters) and larger holes (614 ± 169 vs. 539 ± 0 μm) following the initial surgery compared to those who did not attempt revision surgery. Furthermore, the duration of symptoms was shorter in those who had a successful revision surgery compared to those with an unsuccessful revision surgery (24 ± 21 vs. 46 ± 33 weeks). The failure MH size was also smaller in those who had a successful outcome (559 ± 117 vs. 859 ± 167 μm). Our findings for revision surgery are compatible with those of Fallico et al. [7] for primary surgery, which showed a better visual outcome in those with a shorter duration of symptoms and smaller MH size.

Patients who underwent revision surgery achieved a closure rate of 85%. This is consistent with a previous study by Yek et al. [3] which reported a success rate of 85% (45/53 eyes). At 12 months following revision surgery, we reported a mean BCVA of 55 ± 19 letters (6/24 with the Snellen chart) and a mean change in acuity of +16 ± 17 letters compared to their initial presentation measures before the first surgery. VA also continued to improve over time. Indeed, a study suggests that VA improves up to 2 years after surgery for MH and

stabilizes thereafter [8]. In our study, with only a 12-month follow-up, the BCVA was higher or equal to 6/12 on the Snellen chart in 29% of eyes that had revision surgery.

This is also congruent with a systematic review and meta-analysis by Reid et al. [4], which reported a range of revision surgery closure rates between 44% and 100% with a weighted mean of 75% (n = 389 of 520 eyes). The BCVA 12 months following revision surgery ranged from 26 to 65 letters with a weighted mean of 46 letters (n = 213 eyes). At 24-month follow-up, they showed that 15% of MHs that underwent revision surgery achieved a VA greater than or equal to 6/12 on the Snellen scale.

We also observed a reorganization of the foveal retina layers after the revision surgery (**Figure 3.2**). A larger preoperative MH size before the revision surgery has been associated with worse success in terms of anatomical closure and postoperative VA after the revision surgery [9, 10]. Our study supported these findings as the mean failure MH size was of 559 µm and 859 µm in successful and unsuccessful revision surgeries, respectively. Moreover, an enlargement of the hole is commonly observed after failed surgery. In the study by Yek et al. [3], the mean hole size increased from 426 to 524 µm following the primary failed surgery. This is in contrast to what we observed in our study, in which there was a reduction in the mean hole size from 653 to 614 µm postoperatively.

Our primary MH surgery employed standard methods such as pars plana vitrectomy, removal of posterior hyaloid, ILM peeling (after dye usage), and gas tamponade exchange. Surgical techniques used in the revision surgery included vitrectomy with ILM peeling (remnant peeling or peripheral extension), changing tamponade, inverted flap technique, and ILM transfer (free flap). At the revision surgery of one eye, we used a free flap technique and the MH closed anatomically. However, this eye showed no improvement in VA 6 months after revision surgery and BCVA was counting fingers. Morizane et al. [11] reported a closure rate of 90% (9/10 eyes) and the mean BCVA of 57 ± 67 letters at the 12-month follow-up using free flap technique for revision surgery in large MHs (>400 µm). At the revision surgery of another two eyes, we performed inverted flaps (since we had remnant ILM at the foveal border). These two MHs closed and the BCVA were, respectively, counting fingers and 35 letters at 3 months postoperatively. This method is particularly useful in large MHs but not always possible when complete peeling of ILM was previously done [12]. On the other hand, inverted flap in large MHs (>400 µm) at first surgery showed a closure rate of 95% (95% CI,

88 to 98% with 118 eyes) with BCVA of 51 ± 78 letters at a mean follow-up period of 10.18 ± 4.46 months [13].

Large and persistent MHs remain surgical challenges, which is why new surgical methods continue to be developed. Modified autologous ILM translocation at revision surgery is also possible, but more challenging. Three studies have been published and showed a MH closure rate at revision surgery of 91%, 92%, and 100% with BCVA of 65 ± 71, 41 ± 69, and 35 ± 76 letters for a mean MH size of 512, 655, and 811 μm, respectively. The follow-up period was 8, 12, and 12 months, respectively [14–16].

Grafting with lens capsule is also a technique described by Chen and Yang [17] with closure rate at revision surgery of 67% (6/9 eyes) and BCVA of 37 ± 68 letters at 6 months postoperatively for a mean MH size of 805 μm. This technique is useful when there is a failure of MH closure with ILM peeling and where only minimal ILM is available as a graft.

Induced macular detachment is another technique consisting of injecting the subretinal balanced salt solution. Gurelik et al. [18] reported a closure rate at revision surgery of 100% (7/7 eyes) with subjective improvement in VA. Szigiato et al. [19] showed the same closure rate at revision surgery (8/8 eyes; mean MH size of 699 μm) with BCVA of 30 ± 66 letters at 6 months. In a study by Frisina et al. [20], the hole closure in revision surgery was 90% (9/10 eyes) in eyes with a mean MH size of 230 ± 117 μm at baseline, and BCVA improved to 57 ± 75 letters at 6 months postoperatively.

Macular graft has recently been described for large and refractory MHs. According to Mahmoud and Marlow [21], the macular graft should be considered for refractory MHs or large MHs (≥700 μm). Wu et al. [22] observed a closure rate at revision surgery of 67% (4/6 eyes) in eyes with a mean MH size of 979 ± 441 μm at baseline, and BCVA was 31 ± 59 letters at 12 months of follow-up. In another larger study by Grewal et al. [23], the closure rate at revision surgery was 88% (36/41 eyes) in eyes with a mean MH size at baseline of 825 ± 423 μm, and BCVA was 34 ± 60 letters at 11.1 ± 7.7 months postoperatively.

Finally, various adjuvants (autologous whole blood or serum, autologous platelet concentrate, and TGF-beta) have been used to facilitate hole closure. Functional

improvement and closure rates vary greatly for these adjuvants and little data is available [24].

The main limitations of our study are the small sample size and the retrospective nature of the study with a follow-up of varying duration for different patients. Further randomized controlled trials with a larger sample size are necessary to better understand the value of these new surgical techniques.

In conclusion, there is limited evidence on the management of unclosed MHs after primary surgery. However, the postoperative results after revision surgery in terms of closure rate and improvement of VA lead us to consider revision surgery in the majority of cases. We demonstrated clear benefits in performing revision surgery, with 29% of unclosed MHs after primary surgery achieving BCVA higher or equal to 6/12 after revision surgery. An extension of the ILM peeling with an exchange of tamponade can often be attempted after a failed primary surgery with a fair success rate. Further work would be useful to further evaluate the role of unconventional surgical methods for refractory MH in revision surgery.

3.8 Author contribution statement

AD conceptualized the project and oversaw the execution of the project. AL reviewed the proposal and collected the data. AD and AL analyzed, interpreted, and drafted the manuscript. EY, JG, SB, MC, and ET participated in drafting, reviewing, and editing the article. All coauthors reviewed the manuscript and approved the final manuscript.

3.9 Acknowledgments

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3.10 Data Availability and Conflicts of Interest

The data used to support the findings of this study are available from the corresponding author upon request. The authors declare that there are no conflicts of interest regarding the publication of this paper.

3.11 References

[1] Parravano M., Giansanti F., Eandi C. M., et al. Vitrectomy for idiopathic macular hole. *The Cochrane Database of Systematic Reviews*. 2015;2015(5) doi: 10.1002/14651858.CD009080.pub2.CD009080.

[2] Gaudric A., Tadayoni R. Chapter 117-macular hole. In: Ryan S. J., editor. *Retina*. 5th. Philadelphia, PA, USA: W. B. Saunders; 2013. pp. 1962–1978.

[3] Yek J. T. O., Hunyor A. P., Campbell W. G., et al. Outcomes of eyes with failed primary surgery for idiopathic macular hole. *Ophthalmology Retina*. 2018;2(8):757–764. doi: 10.1016/j.oret.2017.10.012.

[4] Reid G. A., McDonagh N., Wright D. M., Yek J. T. O., Essex R. W., Lois N. First failed macular hole surgery or reopening of a previously closed hole. *Retina*. 2020;40(1):1–15. doi: 10.1097/iae.0000000000002564.

[5] Duker J. S., Kaiser P. K., Binder S., et al. The international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology*. 2013;120(12):2611–2619. doi: 10.1016/j.ophtha.2013.07.042.

[6] Fung N. S. K., Mak A. K. H., Yiu R., Wong I. Y. H., Lam W. C. Treatment of large, chronic and persistent macular hole with internal limiting membrane transposition and tuck technique. *International Journal of Retina and Vitreous*. 2020;6:p. 3. doi: 10.1186/s40942-019-0206-7.

[7] Fallico M., Jackson T. L., Chronopoulos A., et al. Factors predicting normal visual acuity following anatomically successful macular hole surgery. *Acta Ophthalmologica*. 2020 doi: 10.1111/aos.14575.

[8] Karacorlu M., Sayman Muslubas I., Ersoz M. G., Hocaoglu M., Arf S. When does visual acuity stabilize after macular hole surgery? five-year follow-up of surgery for idiopathic macular hole. *Acta Ophthalmologica*. 2019;97(1):e136–e137. doi: 10.1111/aos.13862.

[9] Ullrich S., Haritoglou C., Gass C., et al. Macular hole size as a prognostic factor in macular hole surgery. *British Journal of Ophthalmology*. 2002;86(4):390–393. doi: 10.1136/bjo.86.4.390.

[10] Cheng L., Azen S. P., El-Bradey M. H., et al. Effects of preoperative and postoperative epiretinal membranes on macular hole closure and visual restoration. *Ophthalmology*. 2002;109(8):1514–1520. doi: 10.1016/s0161-6420(02)01093-x.

[11] Morizane Y., Shiraga F., Kimura S., et al. Autologous transplantation of the internal limiting membrane for refractory macular holes. *American Journal of Ophthalmology*. 2014;157(4):861–869. doi: 10.1016/j.ajo.2013.12.028.

[12] Michalewska Z., Michalewski J., Adelman R. A., Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology*. 2010;117(10):2018–2025. doi: 10.1016/j.ophtha.2010.02.011.

[13] Gu C., Qiu Q. Inverted internal limiting membrane flap technique for large macular holes: a systematic review and single-arm meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2018;256(6):1041–1049. doi: 10.1007/s00417-018-3956-2.

[14] Ozdek S., Baskaran P., Karabas L., Neves P. P. A modified perfluoro-n-octane-assisted autologous internal limiting membrane transplant for failed macular hole reintervention: a case series. *Ophthalmic Surgery, Lasers and Imaging Retina*. 2017;48(5):416–420. doi: 10.3928/23258160-20170428-08.

[15] Pires J., Nadal J., Gomes N. L. Internal limiting membrane translocation for refractory macular holes. *The British Journal of Ophthalmology*. 2017;101(3):377–382. doi: 10.1136/bjophthalmol-2015-308299.

[16] Dai Y., Dong F., Zhang X., Yang Z. Internal limiting membrane transplantation for unclosed and large macular holes. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2016;254(11):2095–2099. doi: 10.1007/s00417-016-3461-4.

[17] Chen S.-N., Yang C.-M. Lens capsular flap transplantation in the management of refractory macular hole from multiple etiologies. *Retina*. 2016;36(1):163–170. doi: 10.1097/iae.0000000000000674.

[18] Gurelik G., Sul S., Kılıç G., Özsaygılı C. A modified foveal advancement technique in the treatment of persistent large macular holes. *Ophthalmic Surgery, Lasers and Imaging Retina*. 2017;48(10):793–798. doi: 10.3928/23258160-20170928-03.

[19] Szigiato A.-A., Gilani F., Walsh M. K., Mandelcorn E. D., Muni R. H. Induction of macular detachment for the treatment of persistent or recurrent idiopathic macular holes. *Retina*. 2016;36(9):1694–1698. doi: 10.1097/iae.0000000000000977.

[20] Frisina R., Tozzi L., Sabella P., Cacciatori M., Midena E. Surgically induced macular detachment for treatment of refractory full-thickness macular hole: anatomical and functional results. *Ophthalmologica*. 2019;242(2):98–105. doi: 10.1159/000500573.

[21] Mahmoud T. H., Marlow E. D. Current management strategies for atypical macular holes. *Taiwan Journal of Ophthalmology*. 2020. doi: 10.4103/tjo.tjo_26_20.289057.

[22] Wu A. L., Chuang L. H., Wang N. K., et al. Refractory macular hole repaired by autologous retinal graft and blood clot. *BMC Ophthalmology*. 2018;18(1):p. 213. doi: 10.1186/s12886-018-0898-8.

[23] Grewal D. S., Charles S., Parolini B., Kadonosono K., Mahmoud T. H. Autologous retinal transplant for refractory macular holes: multicenter international collaborative study group. *Ophthalmology*. 2019;126(10):1399–1408. doi: 10.1016/j.ophtha.2019.01.027.

[24] 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. doi: 10.1097/iae.0000000000000948.

3.12 Tables

Table 3.1. Clinical and Demographic Characteristics upon the First Presentation

	MH undergoing revision surgery *n*=20	Successful revision surgery *n*=17	Unsuccessful revision surgery *n*=3	Revision surgery not attempted *n*=2
Age				
Years, mean ± SD	73 ± 6	73 ± 7	73 ± 3	68 ± 13
Sex				
Male, n (%)	7 (35%)	6 (35%)	1 (33%)	2 (100%)
Female, n (%)	13 (65%)	11 (65%)	2 (67%)	0 (0%)
Pseudophakic				
n (%)	4 (20%)	2 (11%)	2 (67%)	1 (50%)
Duration of symptoms				
Weeks, mean ± SD	28 ± 24	24 ± 21	46 ± 33	25 ± 18
Baseline MH size				
µm, mean ± SD	653 ± 231	630 ± 237	781 ± 174	790 ± 170
Failure MH size				
µm, mean ± SD	614 ± 169	559 ± 117	859 ± 167	539 ± 0
VA (letters)				
Baseline, mean ± SD	33 ± 26	33 ± 27	33 ± 23	41 ± 0
Failure, mean ± SD	21 ± 36	24 ± 30	7 ± 63	41 ± 0

MH, macular hole; VA, visual acuity; SD, standard deviation.

Table 3.2. Details of the Revision Surgery Procedure

Features	Successful revision surgery *n*=17	Unsuccessful revision surgery *n*=3
Surgery procedure		
Vitrectomy with extension of ILM peeling, n (%)	12 (70%)	1 (33%)
Changing tamponade with no complementary peeling, n (%)	2 (12%)	1 (33%)
Inverted flap technique, n (%)	2 (12%)	0 (0%)
ILM transfer (free flap), n (%)	1 (6%)	1 (33%)
Tamponade used		
C_3F_8, n (%)	15 (88%)	3 (100%)
Silicone, n (%)	2 (12%)	0 (0%)
Time to reoperation after MH failure		
Months, mean (range)	6 (0.5 – 57)	1 (1 – 2)

MH, macular hole; ILM, internal limiting membrane.

Table 3.3. VA after Revision Surgery

	MH undergoing revision surgery *n*=20	Successful revision surgery *n*=17	Unsuccessful revision surgery *n*=3	Revision surgery not attempted *n*=2
VA (letters)				
Before first surgery, mean ± SD	33 ± 26	33 ± 27	33 ± 23	41 ± 0
Failure, mean ± SD	21 ± 36	24 ± 30	7 ± 63	41 ± 0
3 months after revision surgery	35 ± 32, n = 16	37 ± 31, n = 14	18 ± 46, n = 2	–
Change in letter score, mean ± SD	+3 ± 33	+4 ± 31	-5 ± 64	–
≥0-letter increase, no. (%)	12 (75)	11 (79)	1 (50)	–
≥15-letter increase, no. (%)	5 (31)	4 (29)	1 (50)	–
12 months after revision surgery	55 ± 19, n = 6	55 ± 19, n = 6	N/A	–
Change in letter score, mean ± SD	+16 ± 17	+16 ± 17	N/A	–
≥0-letter increase, no. (%)	5 (83)	5 (83)	N/A	–
≥15-letter increase, no. (%)	3 (50)	3 (50)	N/A	–

VA, visual acuity; MH, macular hole; SD, standard deviation; N/A, not available.

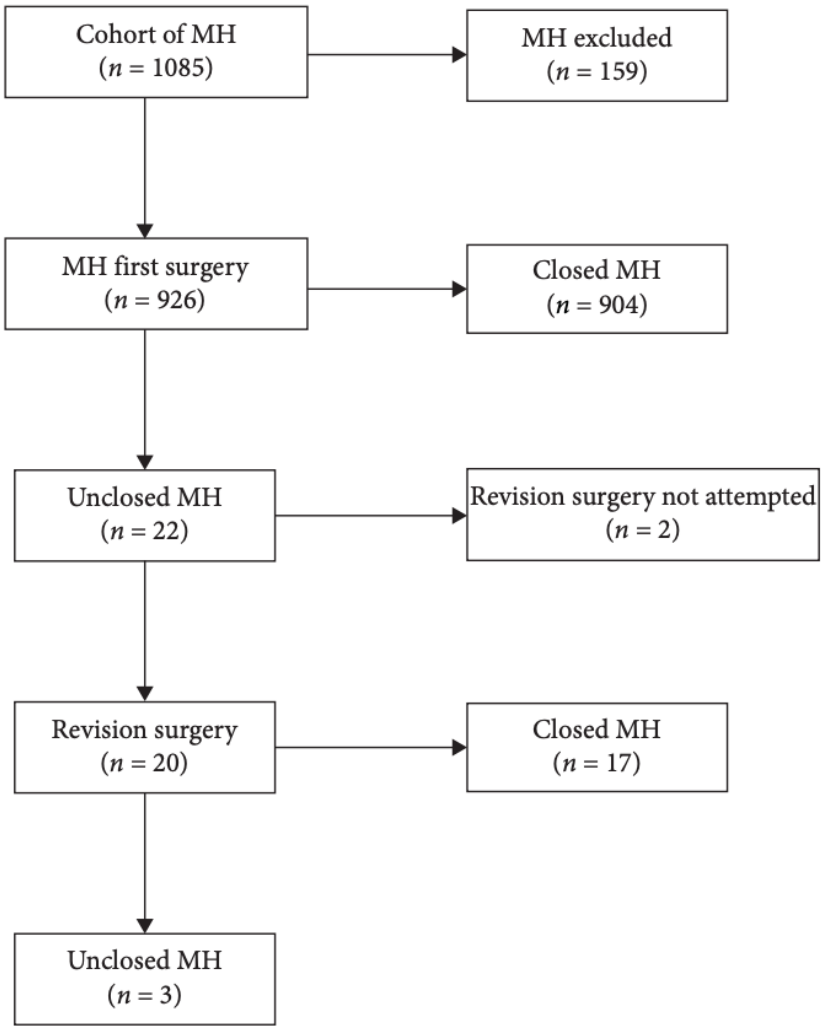
Table 3.4. Evolution of MH Size

	MH undergoing revision surgery *n*=20	Successful revision surgery *n*=17	Unsuccessful revision surgery *n*=3	Revision surgery not attempted *n*=2
MH size before first surgery				
µm, mean ± SD (n)	653 ± 231 (20)	630 ± 237 (17)	781 ± 174 (3)	790 ± 170 (2)
Failure MH size (before revision surgery)				
µm, mean ± SD (n)	614 ± 169 (11)	559 ± 117 (9)	859 ± 167 (2)	539 ± 0 (1)
MH size 1 month after revision surgery				
µm, mean ± SD (n)	102 ± 227 (16)	0 (13)	546 ± 156 (3)	–
MH size 3 months after revision surgery				
µm, mean ± SD (n)	71 ± 245 (12)	0 (11)	849 ± 0 (1)	–
MH size 12 months after revision surgery				
µm, mean ± SD (n)	0 (6)	0 (6)	N/A	–

MH, macular hole; SD, standard deviation; N/A, not available.

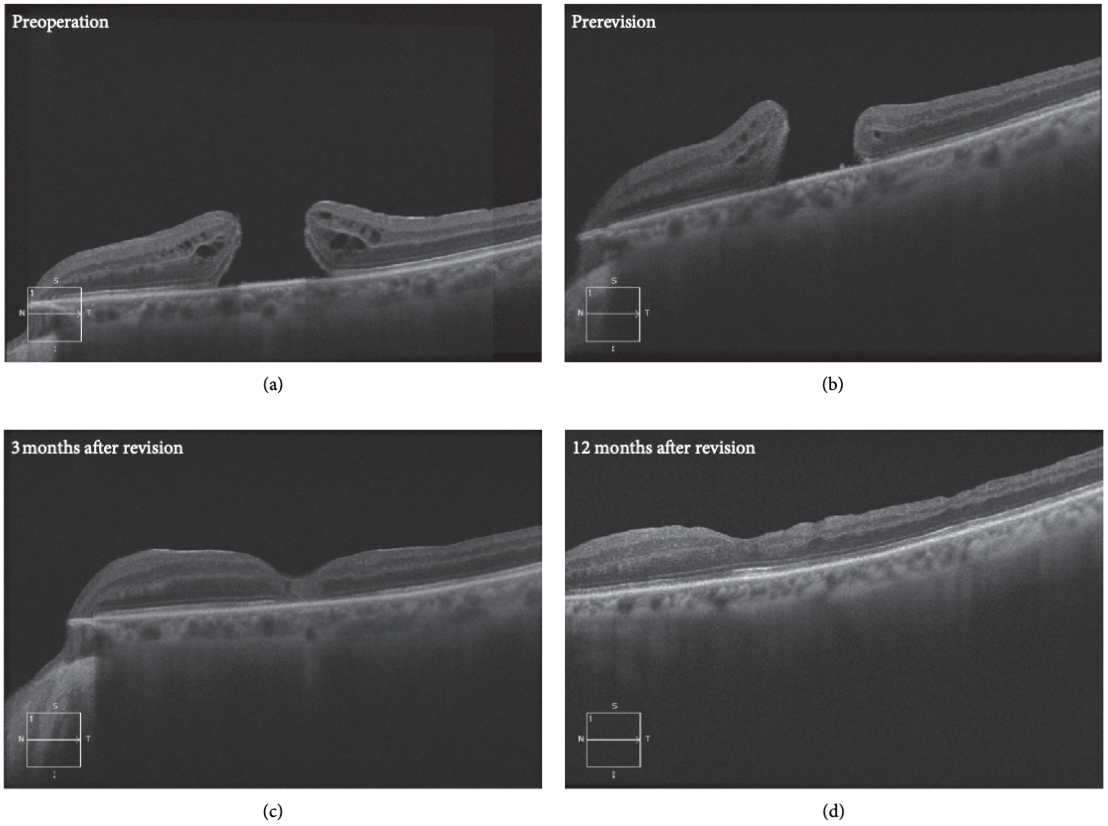
3.13 Figures

Figure 3.1. Flow chart showing management process of eyes undergoing primary and revision surgery



MH, macular hole.

Figure 3.2. Preoperative and postoperative OCT scans



(a) Preoperative OCT scan of an eye with a VA of 41 letters (6/45). (b) OCT scan of an eye prerevision surgery with a VA of hand motion. (c-d) OCT scans 3 and 12 months after successful revision surgery with a VA of counting fingers for both.

Conclusion

C.1 Synthèse des 3 articles présentés

Les facteurs pronostiques de la vision post-opératoire des TM sont principalement le diamètre du TM, l'AV préopératoire et la durée du TM. Bien qu'il existe certaines divergences sur ces facteurs dans la littérature, nous arrivons à la conclusion que ce sont ces trois principaux facteurs qui sont déterminants dans la vision post-opératoire; ces facteurs ont été discutés dans le Chapitre 1. De plus, le statut pseudophaque est important à considérer en préopératoire puisque ces yeux ont une meilleure acuité visuelle finale. Nous avons également identifié une AV préopératoire ≥ 55,5 lettres ETDRS (équivalent Snellen : 6/30) comme un facteur prédictif significatif d'un AV finale ≥ 70 lettres ETDRS et une taille du TM inférieure à 237 µm comme un facteur prédictif significatif d'un gain d'AV ≥ 15 lettres ETDRS.

Ces données cliniques sélectionnées au Chapitre 1 comme étant les plus importantes ont par la suite été intégrées dans un modèle en combinaison avec des HD-OCT préopératoires de TM. Dans ce modèle, l'AP fut utilisé sur l'imagerie pour prédire le gain en AV après la vitrectomie. Cette prédiction par l'AP fut combinée à la prédiction basée sur les données cliniques. La prédiction basée individuellement sur les HD-OCT ou les données cliniques était intéressante, mais la combinaison des données cliniques et de l'imagerie ne permettait pas d'augmenter significativement le potentiel de prédiction. Ainsi, on peut conclure que les données cliniques et l'imagerie ont un potentiel de prédiction similaire et qu'il a de la redondance d'information dans ces deux différentes sources de données (clinique et imagerie).

Nous voulions par la suite investiguer l'issue des yeux qui subissaient un échec à une première VPP afin de mieux prendre en charge ces patients. Nos résultats ont montré qu'une majorité des yeux qui avaient une reprise chirurgicale d'une vitrectomie avec échange de tamponnade réussissaient à fermer chirurgicalement, soit dans 85% (17/20) des cas. Également, ces yeux montraient une amélioration de leur AV au fil du temps. Bien que l'étude présentée au Chapitre 3 soit descriptive, les résultats suggèrent que les patients avec une plus courte durée des symptômes, une meilleure AV avant la chirurgie de révision ainsi qu'un TM de plus faible diamètre ont plus de chance de fermer chirurgicalement à la

suite de la chirurgie de révision. Des techniques chirurgicales plus avant-gardistes ont aussi été discutées selon la littérature actuelle dans le Chapitre 3.

C.2 Limitations

Bien évidemment, les 3 études s'inscrivent dans un devis rétrospectif, ce qui fait en sorte que celles-ci sont sujettes aux biais connus pour ces types d'étude, notamment le suivi de durée variable pour différents patients et la difficulté d'avoir une AV à un moment précis. De même, bien que la collecte de données se soit effectuée dans un des plus grands centres en ophtalmologie au Canada, il demeure que la quantité de données reste limitée en ce qui concerne le développement du modèle hybride d'intelligence artificielle particulièrement. L'intelligence artificielle nécessite la plupart du temps une quantité de données non négligeable afin d'arriver à un potentiel de prédiction intéressant. Cependant, nous sommes parvenus à des résultats satisfaisants avec l'ensemble des données dont nous disposions.

C.3 Perspectives

En ce qui concerne les facteurs pronostiques et le potentiel de prédiction de notre modèle hybride d'intelligence artificielle, il serait intéressant de perfectionner ce modèle pour parvenir à augmenter davantage le potentiel de prédiction par le biais des alternatives présentées dans la discussion du Chapitre 2. Il serait aussi très intéressant de mieux comprendre les mécanismes qui guident les prédictions de ce modèle. Il s'agit là d'un problème courant en intelligence artificielle, les modèles fournissent de prime abord peu d'explication sur leur façon de faire les prédictions. Enfin, en ce qui a trait aux TM subissant un échec à la fermeture chirurgicale d'une première VPP, davantage d'étude de qualité et avec de plus grands échantillons sont requis pour mieux apprécier le pronostic visuel de la reprise chirurgicale selon les différentes techniques chirurgicales.

Bibliographie

[1] Johnson MW. Posterior vitreous detachment: evolution and complications of its early stages. *American Journal of Ophthalmology*. 2010 Mar;149(3):371-82.e1. doi: 10.1016/j.ajo.2009.11.022. PMID: 20172065.

[2] Patel H, Congdon N, Strauss G, et al. A Need for Standardization in Visual Acuity Measurement. *Arquivos Brasileiros de Oftalmologia*. 2017; 80 (5): 332-337.

[3] Chen AH, Norazman FN, Buari NH. Comparison of visual acuity estimates using three different letter charts under two ambient room illuminations. *Indian Journal of Ophthalmology*. 2012; 60 (2): 101–104.

[4] Shamir RR, Friedman Y, Joskowicz L, et al. Comparison of Snellen and Early Treatment Diabetic Retinopathy Study charts using a computer simulation. International *Journal of Ophthalmology*. 2016; 9 (1): 119–123.

[5] Laidlaw DA, Abbott A, Rosser DA. Development of a clinically feasible logMAR alternative to the Snellen chart: performance of the “compact reduced logMAR” visual acuity chart in amblyopic children. *The British Journal of Ophthalmology*. 2003; 87:1232-1234.

[6] Rosser DA, Laidlaw DA, Murdoch IE. The development of a “reduced logMAR” visual acuity chart for use in routine clinical practice. *The British Journal of Ophthalmology*. 2001; 85: 432-436.

[7] Kaiser PK. Prospective evaluation of visual acuity assessment: a comparison of snellen versus ETDRS charts in clinical practice (An AOS Thesis). *Transactions of the American Ophthalmological Society*. 2009; 107: 311-24.

[8] Yu HJ, Kaiser PK, Zamora D, et al. Visual Acuity Variability: Comparing Discrepancies between Snellen and ETDRS Measurements among Subjects Entering Prospective Trials. *Ophthalmology Retina*. 2020; S2468-6530 (20): 30154-8.

[9] Rosser DA, Cousens SN, Murdoch IE, et al. The development of a “reduced logMAR” visual acuity chart for use in routine clinical practice. *Investigative Ophthalmology & Visual Science*. 2003; 44 (8): 3278-3281.

[10] Elliott DB, Sheridan M. The use of accurate visual acuity measurements in clinical anti-cataract formulation trials*. Ophthalmic & Physiological Opticals*. 1988; 8 (4): 397-401.

[11] Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *Retina*. 2010; 30 (7): 1046-1050.

[12] JT Holladay. Proper method for calculating average visual Acuity. *Journal of Refractive Surgery*. 1997; 13 (4): 388-91.

[13] Rahmani B, Tielsch JM, Katz J, et al. The cause-specific prevalence of visual impairment in an urban population. *Ophthalmology*. 1996 ; 103 (11) : 1721-1726.

[14] Mitchell P, Smith W, Chey T, et al. Prevalence and associations of epiretinal membranes. The Blue Mountains Eye Study. *Australia Ophthalmology*. 1997; 104 (6): 1033-1040.

[15] Wang S, Xu L, Jonas JB. Prevalence of full-thickness macular holes in urban and rural adult Chinese: the Beijing Eye Study. *American Journal of Ophthalmology*. 2006; 141 (3): 589-591.

[16] Sen P, Bhargava A, Vijaya L, et al. Prevalence of idiopathic macular hole in adult rural and urban south Indian population. *Clinical & Experimental Ophthalmology*. 2008; 36 (3): 257-260.

[17] Klein R, Klein BE, Wang Q, et al. The epidemiology of epiretinal membranes. *Transactions of the American Ophthalmological Society*. 1994; 92: 403–430.

[18] McCannel CA, Ensminger JL, Diehl NN, et al. Population-based incidence of macular holes. *Ophthalmology*. 2009; 116: 1366–1369.

[19] The Eye Disease Case–Control Study Group. Risk factors for idiopathic macular holes. *American Journal of Ophthalmology*. 1994; 118 (6): 754-76.

[20] Evans JR, Schwartz SD, McHugh JD, et al. Systemic risk factors for idiopathic macular holes: a case–control study. *Eye*. 1998; 12: 256-259.

[21] Shah SP, Bunce C, Johnston RL, et al. Are biometric parameters a risk factor for idiopathic macular hole formation? Results of a matched case–control series. *The British Journal of Ophthalmology*. 2006; 90 (1): 117-118.

[22] Parravano M, Giansanti F, Eandi CM, et al. Vitrectomy for idiopathic macular hole. *The Cochrane Database of Systematic Reviews*. 2015; CD009080.

[23] Takahashi A, Yoshida A, Nagaoka T, et al. Macular hole formation in fellow eyes with a perifoveal posterior vitreous detachment of patients with a unilateral macular hole. *American Journal of Ophthalmology*. 2011; 151 (6): 981-989.

[24] Takahashi A, Nagaoka T, Ishiko S, et al. Foveal anatomic changes in a progressing stage 1 macular hole documented by spectral-domain optical coherence tomography. *Ophthalmology*. 2010; 117 (4): 806-810.

[25] Gaudric A et Tadayoni R. « Macular hole », dans *Retina*, SJ Ryan, 5^{e} éd, Vol. 5, p. 1962-1978. Saunders, Philadelphie, PA, États-Unis, 2013.

[26] Gass JD. Idiopathic senile macular hole. Its early stages and pathogenesis. *Archives of Ophthalmology*. 1988; 106:629-39.

[27] Chan A, Duker JS, Schuman JS, et al. Stage 0 macular holes: observations by optical coherence tomography. *Ophthalmology*. 2004; 111 (11): 2027-2032.

[28] Gaudric A, Haouchine B, Massin P, et al. Macular hole formation: new data provided by optical coherence tomography. *Archives of Ophthalmology*. 1999; 117 (6): 744-751.

[29] Haouchine B, Massin P, Gaudric A. Foveal pseudocyst as the first step in macular hole formation: a prospective study by optical coherence tomography. *Ophthalmology*. 2001; 108 (1): 15-22.

[30] Takahashi A, Nagaoka T, Yoshida A. Stage 1-A macular hole: a prospective spectral-domain optical coherence tomography study. *Retina*. 2011; 31 (1): 127-147.

[31] 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.

[32] Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. *Archives of Ophthalmol*ogy. 1991; 109 (5): 654-659.

[33] Scott IU, Moraczewski AL, Smiddy WE, et al. Long-term anatomic and visual acuity outcomes after initial anatomic success with macular hole surgery. *American Journal of Ophthalmology*. 2003; 135 (5): 633-640.

[34] Yek JTO, Hunyor AP, Campbell WG, et al. Outcomes of Eyes with Failed Primary Surgery for Idiopathic Macular Hole. *Ophtalmology Retina*. 2018; 2: 757-764.

[35] Bikbova G, Oshitari T, Baba T, Yamamoto S & Mori K. Pathogenesis and Management of Macular Hole: Review of Current Advances. *Journal of ophthalmology*. 2019: 3467381.

[36] Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science.* 1991; 254(5035): 1178-81.

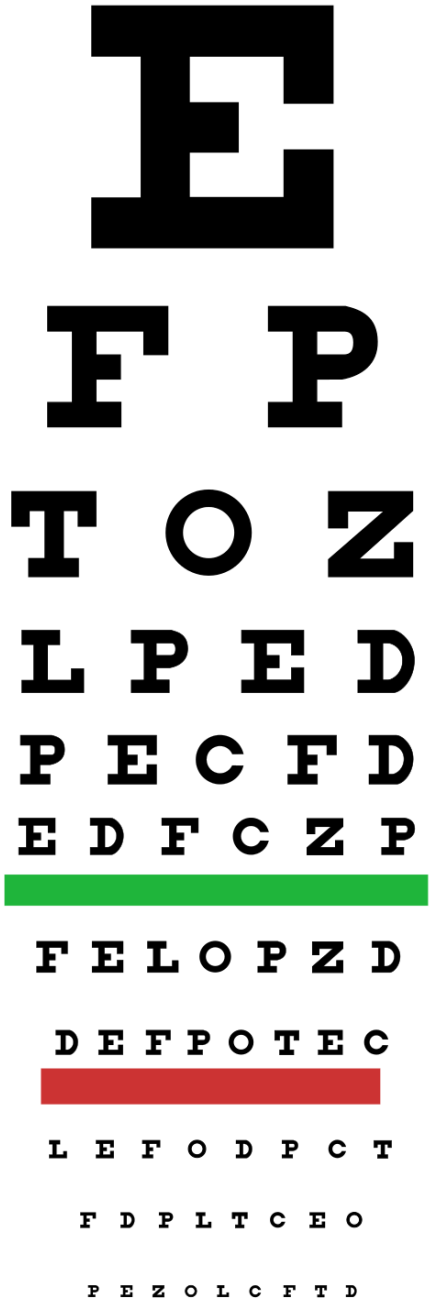
[37] Chang YC, Lin WN, Chen KJ, et al. Correlation Between the Dynamic Postoperative Visual Outcome and the Restoration of Foveal Microstructures After Macular Hole Surgery. *American Journal of Ophthalmology*. 2015; 160(1): 100-6.e1.

[38] Ittarat M, Somkijrungroj T, Chansangpetch S & Pongsachareonnont P. Literature Review of Surgical Treatment in Idiopathic Full-Thickness Macular Hole. *Clinical ophthalmology* (Auckland, N.Z.). 14:2171–2183.

[39] Streho M & Matonti F. Techniques et principes des tomographies en cohérence optique. *Encyclopédie médico-chirurgicale*. 2017. Elsevier Paris, 9. ; Ophtalmologie, 21-045-A-15.

[40] Essex RW, Hunyor AP, Moreno-Betancur M, et al. Australian and New Zealand Society of Retinal Specialists Macular Hole Study Group. The visual outcomes of macular hole surgery: a registry-based study by the Australian and New Zealand society of retinal specialists. *Ophthalmology Retina*. 2018; 2: 1143–1151.

Annexe A - Échelle de Snellen



1	20/200
2	20/100
3	20/70
4	20/50
5	20/40
6	20/30
7	20/25
8	20/20
9	
10	
11	

Wikipedia. (2020, 1 août). *Snellen Chart* [Image]. Snellen Chart. https://en.wikipedia.org/wiki/Snellen_chart#/media/File:Snellen_chart.svg

Annexe B - Échelle ETDRS

Precision Vision. (2020, 1 août). *Original Series Sloan Letter ETDRS* [Image]. Precision Vision. https://www.precision-vision.com/products/etdrs/etdrs-charts/original-series-sloan-letter-etdrs-charts/original-series-sloan-letter-etdrs-chart-21/