Predictive Factors of the Anatomical and Functional Success of Macular Hole Surgery

Fatores Preditores do Sucesso Anatómico e Funcional da Cirurgia do Buraco Macular

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ABSTRACT

INTRODUCTION: Idiopathic macular hole (iMH) is a vitreoretinal interface pathology which is treatment is surgical-based. Currently, the anatomical success rate of the surgery varies between 85% and 100%, however, the functional recovery of visual acuity may be limited despite successfully closing the iMH.

Our purpose was to identify preoperative factors that better predict the anatomical and functional success of iMH surgery.

METHODS: Retrospective cohort study of patients submitted to pars plana vitrectomy for iMH treatment aided by peeling of the internal limiting membrane or inverted flap technique, between January 2015 and December 2019, at Hospital de Braga. The following parameters were evaluated: age, sex, best preoperative corrected visual acuity (preBCVA), time spent from diagnosis to surgery (TTS), iMH size, presence of concomitant epiretinal membrane or adherent posterior hyaloid membrane (PHM) and surgical technique used. The correlation between the described parameters and the anatomical surgical success and the postoperative BCVA (functional success) was evaluated.

RESULTS: Seventy-one eyes of 67 patients were included, with female predominance (71.6%) and a mean age of 68.3 ± 8.3 years at diagnosis. Anatomical success was obtained in 70.4% eyes and none of the factors analyzed had a statistically significant impact on the anatomical success of the surgery. On the other hand, it was observed that preBCVA (b = 0.540; t = 5.371; p <0.001), TTS (b = 0.001; t = 2.203; p = 0.031) and adherent PHM (b = -0.258; t = -2.098; p = 0.043) had a significant impact on postoperative BCVA. Multivariate linear regression analysis showed that only preBCVA had an impact in predicting functional recovery (b = 0.381; t = 2.784; p = 0.009).

CONCLUSION: Preoperative visual acuity is the best predictor of the functional success of iMH surgery, suggesting that it allows a better management of patient´s pre-surgical expectations.

KEYWORDS: Retinal Perforations/diagnosis; Retinal Perforations/epidemiology; Retinal Perforations/surgery.

RESUMO

INTRODUÇÃO: O buraco macular idiopático (BMi) é uma patologia da interface vítreo-retiniana cujo tratamento é cirúrgico. Atualmente, a taxa de sucesso anatómico da cirurgia varia entre 85% e 100%, contudo a recuperação funcional da acuidade visual pode ser limitada apesar do sucesso no encerramento da solução de continuidade.

O nosso objetivo foi identificar fatores pré-operatórios preditores do sucesso anatómico e funcional da cirurgia do BMi.

MÉTODOS: Estudo coorte retrospetivo de doentes diagnosticados com BMi e submetidos a vitrectomia via *pars plana* auxiliada por *peeling* da membrana limitante interna ou técnica de *flap* invertido, entre janeiro de 2015 e dezembro de 2019, no Hospital de Braga. Foram avaliados os seguintes parâmetros: idade, sexo, tempo de espera cirúrgico (TCC), melhor acuidade visual corrigida (MAVC) pré-operatória, tamanho do BMi, presença de membrana epiretiniana ou membrana hialóide posterior (MHP) aderente e técnica cirúrgica utilizada. A correlação entre os parâmetros descritos e o sucesso cirúrgico anatómico e a MAVC pós-operatória foi avaliada.

RESULTADOS: Nos 71 olhos de 67 doentes analisados verificou-se uma predominância do sexo feminino (71,6%) e uma idade média ao diagnóstico de 68,3 ± 8,3 anos. Foi identificado sucesso anatómico em 70,4% dos casos, não tendo existido qualquer associação estatística com os fatores analisados. Por outro lado, observou-se que a MAVC pré-operatória (b = 0,540; t = 5,371; $p < 0,001$), o TCC (b = 0,001; t = 2,203; $p = 0,031$) e a MHP aderente (b = -0,258; t = -2.098; $p = 0,043$) apresentaram impacto significativo na MAVC pós-operatória. A análise de regressão linear multivariada evidenciou que apenas a MAVC pré-operatória manteve impacto estatisticamente significativo na predição da recuperação funcional (b = 0,381; t = 2,784; $p = 0,009$).

CONCLUSÃO: A MAVC pré-operatória é o melhor fator preditor do sucesso funcional da cirurgia do BMi, sugerindo-se que permite melhorar a gestão de expectativas pré cirúrgicas.

PALAVRAS-CHAVE: Perfurações Retinianas/cirurgia; Perfurações Retinianas/diagnóstico; Perfurações Retinianas/epidemiologia.

INTRODUCTION

Macular hole (MH) is a solution of continuity of all retinal layers in the macular region and the main cause is idiopathic, with greater predilection for individuals in the sixth and seventh decades of life.[1-3]

Regarding the size of the defect, The International Vitreomacular Traction Study (IVTS) Group classified MH as small (≤ 250 μm), medium (250-400 μm) and large (> 400 μm).[4]

Surgery is the treatment of choice, aiming the correction of macular anatomy in order to improve vision or to prevents its future deterioration.[5] Currently, pars plana vitrectomy (PPV) with inner limiting membrane (ILM) peeling is the *gold standard* technique with a reported anatomical success rate between 85% and 100%.[5-8] Other techniques include inverted flap and ILM graft (mostly used for refractory MH).[9,10] The main postoperative complications include the persistence of the MH and the absence of functional recovery.[11-13]

Current literature identifies the following factors as predictors of anatomical and functional surgical outcome: size, configuration, and stage of the MH; preoperative best corrected visual acuity; and time spent form onset of symptoms to surgery.[12-17] Most of these studies have limitations about sample size.

In this sense, this study aims to identify the factors that better predict the anatomical and functional surgical success of MH surgery to provide a more individualized analysis of the risks and benefits of surgical intervention and, thus, allow a better selection of patients for PPV.

MATERIAL AND METHODS

We performed a retrospective observational cohort study that included all patients diagnosed with idiopathic MH who underwent PPV (alone or combined with phacoemulsification), between January 2015 and December 2019, at Hospital de Braga.

Patients with < 50 years-old, presence of ophthalmologic or systemic diseases with potential interference in the surgical result (e.g., high myopia, retinal detachment, or ocular trauma), traumatic MH, surgical re-interventions, intra or postoperative complications influencing the outcome, and lack of appropriate follow-up, were excluded from this study.

The study was approved by the *Comissão de Ética do Hospital de Braga* (CEHB) and by the *Comissão de Ética para a Investigação das Ciências da Vida e da Saúde* (CEICVS) of the

Universidade do Minho (UM) and follows the tenets of the Declaration of Helsinki. Clinical information was properly coded, ensuring patient confidentiality and anonymity.

The primary outcomes were anatomical success (defined by the observation of a retinal defect closure using spectral-domain optical coherence tomography – SD-OCT – the remaining statistical study did not include cases in which anatomical success was not verified) and functional success (BCVA progression). Data were collected in the following time periods: preoperatively and 3-6 months, 6-9 months, 9-12 months, 12-18 months, and 18-24 months after surgery.

Demographic data, concomitant ocular, or systemic disease, affected eye, MH tomographic parameters, surgical technique, and intra and postoperative complications were also registered. Time to surgery (TTS) was calculated, in days, from the confirmation of the MH diagnosis to the surgical intervention.

Tomographic MH findings were evaluated using SD-OCT preoperatively (MH size, presence of parafoveal cysts, presence of concomitant epiretinal membrane (ERM) or adherent posterior hyaloid membrane (PHM)) and postoperatively (MH closure).

SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY

The high-resolution Spectralis SD-OCT tomography (Heidelberg Engineering, Heidelberg, Germany) was used to gather images of the macula, using the FAST protocol, obtaining a 20x20° macular square centered on the fovea, consisting of 25 horizontal slices with 240 μm between them. Each B-scan was processed 9 times (ART 9). Additionally, a single vertical and horizontal scan centered on the fovea was acquired in enhanced depth imaging mode and processed 100 times (ART 100). MH size was measured manually, using high-definition horizontal scan, as the closest horizontal distance between the edges of the MH, and then classified according to the IVTS classification. The presence of ERM was assessed by observing an hyperreflective line over the ILM with wrinkling of this layer. PHM was detected as the presence of an intermediate reflectivity line in the vitreous cavity or adherent to the ILM. Anatomical success was assumed as closure of the defect seen in SD-OCT, defined as the absence of complete disruption of the retinal layers in the subfoveal region.

SURGICAL PROCEDURE

All surgeries were performed by a total of 6 vitreoretinal surgeons. All phakic patients aged ≥ 50 years underwent phacoemulsification and concomitant intraocular lens placement. The PPV technique consisted of three 23-gauge incisions 3.5-4.0 mm from the limbus. Central vitrectomy guided by triamcinolone was performed and, in the presence of ERM, it was peeled in the macular area, approximately up to the vascular arcades, with the aid of Brilliant-Blue FCF® dye. All cases were complemented by the ILM peeling or the inverted flap technique. The surgical technique used was decided according to the surgeon's preference. The ILM peeling technique was performed from the foveal region to the vascular arcades, and in the inverted flap technique, the ILM was left adherent to the edges of the fovea and the remnants were introduced into the MH´s bed. The retinal periphery was reviewed 360° wide and any retinal defect was submitted to perilesional retinopexy with endocular LASER. After fluid-air exchange, the tamponade material was left to the surgeon´s choice – sulfur hexafloride (SF6), hexafluoroethane (C2F6) or perfluoropropane (C3F8). Postoperatively, patients were instructed to perform ventral positioning for a maximum period of 5 days.

STATISTICAL ANALYSIS

Data were analyzed using the Statistical Package for the Sciences Software (IBM, version 25.0; USA). BCVA (Snellen decimal scale) was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical purposes. The normality of quantitative variables was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The evaluation of BCVA at different moments of the follow-up was carried out using Friedman test. For the comparison of the same variable in only two temporal moments, the Wilcoxon Signed-Rank test was used. The impact of categorical variables on anatomical success was assessed using Chi-square test or Fisher´s exact test – test selection considered Cochran´s rules. The impact of quantitative variables on anatomical success was assessed using the Mann-Whitney test. The effect of the same independent variable on postoperative BCVA was evaluated by univariate and multivariate linear regression. A p-value of < 0.05 was considered statistically significant. In tests of multiple comparisons, the p-value was adjusted using Bonferroni correction.

RESULTS

A total of 71 eyes of 69 patients that underwent PPV for treatment of idiopathic MH were obtained. At diagnosis, the mean age was 68.3 ± 8.3 years-old, with a statistically significant female predominance (71.6%, $p < 0.001$). The median TTS was 88 days (IQR = 118). Most eyes (81.3%) did not have concomitant ERM ($p < 0.001$). Adherent PHM was detected in 48.4% eyes. Anatomical success was obtained in 70.4% eyes – anatomical failure cases were excluded from the functional/visual statistical study and results. Regarding the surgical procedure, the ILM peeling technique was performed in 24 (33.8%) eyes and the inverted flap technique in 43 (60.6%) eyes. The number of patients submitted to ILM graft was significantly lower than other techniques, with only 4 eyes. These patients were excluded from data. Table 1 summarizes the descriptive analysis of the sample.

Table 1. Descriptive analysis.	
Parameter	**Sample**
Eyes / Patients (n)	71 / 69
Age at diagnosis (M +- SD, years)	68.3 +- 8.25
Gender - male [n (%)]	48 (71.6)
Eye - OD [n (%)]	28 (39.4)
TTS [Mdn (IQR), days]	88 (118)
MH size [(n (%)]	
Small	12 (18.8)
Medium	13 (20.3)
Large	39 (60.9)
Presence of ERM [n (%)]	12 (18.7)
Adherent PHM [n (%)]	31 (48.4)
Surgical technique [n (%)]	
ILM peeling	24 (33.8)
IF	43 (60.6)
ILM graft	4 (5.6)
Concomitant phacoemulsification [n (%)]	46 (64.8%)
Anatomical success [n (%)]	50 (70.4)

n – absolute frequency; M – mean; SD – standard deviation; TTS – time to surgery; Mdn – median; MH – macular hole; IQR – interquartile range; ERM – epiretinal membrane; PHM – posterior hyaloid membrane; ILM – internal limiting membrane; IF – inverted flap.

VISUAL RESULTS

Baseline BCVA had a median of 1.00 (IQR = 0.60) logMAR. Visual acuity assessment during follow-up is shown in Fig. 1-A. Since no statistically differences were identified in BCVA through the 5 postoperative time periods, postoperative BCVA (postBCVA) in the last postoperative evaluation was considered, representing a 0.50 median value (IQR = 0.70) in logMAR. PostBCVA was significantly better then preBCVA ($p < 0.001$).

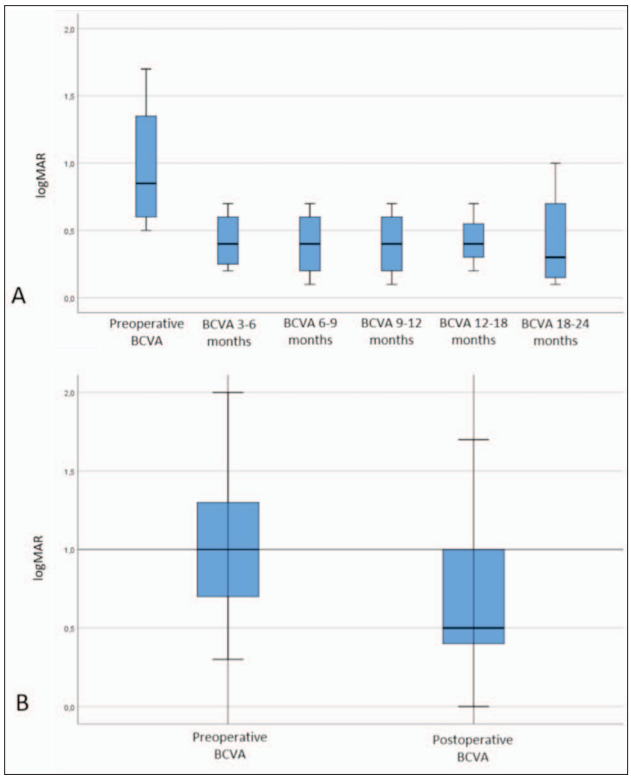

Figure 1. A – Extremum and quartile diagram representative of logMAR BCVA for different follow-up times before and after surgery; B – Extremum and quartile diagram representative of preBCVA and postBCVA.

IDENTIFICATION OF PREDICTORS WITH AND IMPACT ON ANATOMICAL SUCCESS

The impact of the following variables on the anatomical success was evaluated: age, gender, TTS, preBCVA, MH size, presence of ERM or adherent PHM, surgical technique used, and concomitant phacoemulsification. Table 2 shows the univariate analysis of the impact of the aforementioned

Table 2. Univariate analysis of the impact of different variables on the anatomical success.			
Parameter	**Anatomical Success**	**No Anatomical Success**	**Test statistics**
Age (Mdn, years)	70	66	U = 339.50; p = 0.092; r = -0.21
Gender - male (n)	13	5	$\chi^2(1) = 0.007$; p = 0.93; $\phi = 0.010$
TTS (n, days)	102.5	86	U = 389.00; p = 0.489; r = 0.09
preBCVA (Mdn, logMAR)	1.0	1.0	U = -0.94; p = 0.34; r = -0.12
MH size (Mdn, μm)	484	398	U = -314.50; p = 0.097; r = -0.21
Presence of ERM (n)	8	4	Fisher´s exact test, p = 0.74; $\phi = 0.038$
Adherent PHM (n)	26	7	$\chi^2(1) = 2.34$; p = 0.13; $\phi = 0.19$
Surgical technique (n)			
ILM peeling	15	9	$\chi^2(1) = 0.925$; p = 0.34; $\phi = 0.118$
IF	31	11	
Concomitant phacoemulsification (n)	28	18	$\chi^2(1) = 2.712$; p = 0.10; $\phi = -0.238$

n – absolute frequency; OD – oculus dextrus; OS – oculus sinistre; preBCVA – preoperative best corrected visual acuity; Mdn – median; ERM – epiretinal membrane; PHM – posterior hyaloid membrane; ILM – internal limiting membrane; IF – inverted flap

Table 3. Logistic regression models to assess the impact of different factors on the anatomical success.

Parameter	B (SE)	Wald (df=1)	*p*-value	OR (IC 95%)
Age	0.088 (0.061)	2.115	0.146	1.092 (0.970 ; 1.230)
Gender	1.052 (0.912)	1.329	0.249	2.862 (0.479 ; 17.101)
TTS	0.009 (0.006)	2.683	0.101	1.009 (0.998 ; 1.021)
preBCVA	- 0.123 (0.648)	1.025	0.904	0.884 (0.119 ; 6.588)
MH size				
Small	0.031 (1.110)	0.001	0.978	1.032 (0.117 ; 9.078)
Large	0.905 (1.047)	0.747	0.387	2.473 (0.318 ; 19.263)
ERM	-1.568 (0.958)	2.677	0.102	0.209 (0.032 ; 1.364)
Adherent PHM	-1.030 (0.718)	2.058	0.151	0.357 (0.087 ; 1.458)
Surgical Technique	1.653 (0.881)	3.518	0.061	5.222 (0.928 ; 29.375)
Concomitant phacoemulsification	-1.890 (1.037)	3.322	0.068	0.151 (0.020 ; 1.153)

TTS – time to surgery; preBCVA – preoperative best corrected visual acuity; MH – macular hole; ERM – epiretinal membrane

factors, in which there were no statistically significant associations. Based on logistic regression models, there was no statistically significant impact between any of the variables and the anatomical success (Table 3).

IDENTIFICATION OF PREDICTORS WITH AN IMPACT ON FUNCTIONAL SUCCESS

The impact of the same variables on functional success (visual acuity) was evaluated. Table 4 shows, using univariate analysis, the significant impact of preBCVA (b = 0.506; t = 4.138; $p < 0.001$); TTS (b = 0.001; t=2.368; $p = 0.023$); and Adherent PHM (b = -0.258; t = -2.098; $p = 0.043$) on postBCVA. A multivariate linear regression analysis was performed (Table 5 – only with the factors that demonstrated a significant impact in the univariate analysis described above), in which only preBCVA maintained a statistically significant impact on the prediction of postBCVA (b = 0.381; t = 2.784; $p = 0.009$).

Table 4. Univariate linear regression models to assess the impact of different factors on the functional success of surgery.

Parameter	B (SE)	ß	T	*p*-value	Adjusted R^2
Age	0.007 (0.007)	0.144	0.930	0.358	-0.003
Gender	- 0.173 (0.136)	- 0.195	- 1.276	0.209	0.015
TTS	0.001 (< 0.001)	0.347	2.368	**0.023***	0.099
preBCVA	0.506 (0.122)	0.552	4.138	**< 0.001***	0.287
MH size					
Small	-0.217 (0.161)	-0.207	-1.352	0.184	0.019
Large	0.173 (0.124)	0.214	1.399	0.169	0.022
ERM	0.175 (0.133)	0.169	1.317	0.193	0.012
Adherent PHM	-0.258 (0.123)	-0,.322	-2.098	**0.043***	0.080
Surgical technique	0.174 (0.130)	0.205	1.340	0.188	0.019
Concomitant phacoemulsification	-0.002 (0.110)	-0.003	-0.021	0.983	-0.018

TTS – time to surgery; preBCVA – preoperative best corrected visual acuity; MH – macular hole; ERM – epiretinal membrane; * - statistically significant.

Table 5. Multivariate linear regression analysis to assess the impact of preBCVA and TTS on the functional success of surgery.

Parameter	B (SE)	ß	T	*p*-value	Adjusted R^2
preBCVA	0.381 (0.165)	0.416	2.784	**0.009***	0.323
TTS	0.001 (< 0.001)	0.205	1.414	0.166	
Adherent PHM	-0.184 (0.111)	-0.230	-1.660	0.106	

TTS – time to surgery; preBCVA – preoperative best corrected visual acuity; * - statistically significant.

DISCUSSION

MH is a vitreoretinal pathology with a significant impact on visual acuity and a considerable prevalence in the population. In recent years, the advancement of high-resolution imaging techniques such as OCT has enabled a more detailed assessment of the MH, facilitating the diagnosis, classification and unequivocal documentation of the

anatomical success or failure of the surgery.[8,14,18] Advances have also been made in MH surgery, notably the introduction of ILM peeling, which significantly increased closure rate and improved visual results.[11,19,20] In many cases, there is a discrepancy between morphological and functional recovery, leading to unsatisfactory results that do not correspond to pre-surgical expectations.[14,20] In this study, preoperative visual acuity was the most important predictive factor for functional success after MH surgery.

Demographic results showed a predominance in women with a mean age of 68.3 years which agrees with published literature, that reports a higher prevalence in women in their sixth and seventh decades of life.[1-3]

Technical advances in recent years allow for a reported closure rate between 85% and 100%.[6-8] In this study, the anatomical success rate after surgery was 70.4%, however it is well established that the closure rates vary considerably between studies, depending on patient selection and sample size.[22] Additionally, the definition of surgical success varies according to the literature. The challenge of objectively determining the real time from MH emergence until surgery and the performance of PPV by 6 different surgeons may also have influenced the results.

There was a continuous improvement of BCVA during the follow-up, which agrees with most published studies that point to a continuous improvement over a period of up to 12 months or more.[23,24] Despite this improvement, no significant differences were observed in BCVA through the 5 postoperative time periods evaluated.

Concomitant phacoemulsification had no impact on the functional outcome, probably because most of these patients had incipient cataract, with low functional benefit attributable to phacoemulsification.

None of the factors evaluated had predictive value for anatomical success. On the other hand, three parameters – preBCVA, TTS and adherence of the PHM – proved to be statistically significant predictors of visual results. Using a multivariate linear regression, we verified that preBCVA is the parameter with the highest predictive value in the visual outcome (better preBCVA predicts better postBCVA, with a preBCVA of 1 logMAR predicting a postBCVA of 0.64 logMAR and a preBCVA of 0.4 logMAR predicting a postBCVA of 0.31 logMAR, according to the regression equation – 0.097 + 0.540 x preBCVA, in logMAR). Other studies also showed that preoperative visual acuity has a high predictive value for functional success.[22,25,26]

Most studies demonstrate that the time from symptoms onset to surgical intervention is a good predictor of the anatomical and functional success, with shorter times associated with better results.[14,22,27-29] These results seem to disagree with those we obtained regarding anatomical success, however it is important to note that we considered the time elapse between the definitive diagnosis and the surgery (TTS), which could not reflect the actual interval since the emergence of the MH, whereas in other studies, the onset of symptoms was considered as the starting point, which depends on subjective estimation of the patient. On the other hand, like in other studies, TTS was significantly associated with postBCVA, suggesting that eyes with a shorter waiting time will obtain better functional results – however this relationship did not maintain statistical significance in the multivariate analysis.

The association between structural parameters of the MH assessed by OCT and surgical outcomes is already extensively documented, with several studies supporting the hypothesis that MH size is an important predictor of anatomical closure and functional improvement, with the advantage of being an objective and reproducible measure.[11,12,15,25-27,30,31] We evaluated the correlation between the closest horizontal distance to the parafoveal edges in the MH and the surgical outcomes and, unlike previous studies, MH size did not prove to be a good predictor of neither the anatomical nor the functional surgical success.

The association between ERM and MH is still controverse in literature. The presence of tangential pulling forces on the macula may reduce closure rates.[32,33] Some studies[23,34-37] suggest ERM peeling as an important step for surgical success, while a more recent study[38] shows no benefit (nor harm) to visual or anatomical results when the ERM is removed. In our study, the presence of ERM had no impact on the surgical results.

In our study, the absence of preoperative adherent PHM predicted a better functional outcome in the univariate analysis (this association did not occur in the multivariate analysis). Data concerning this association is scarce in the literature. However, an adherent PHM may reflect greater retinal adhesion and vitreomacular traction and greater propensity to damage during surgery-induced hyaloid detachment, compromising the functional success of the surgery.[39]

The last factor analyzed was the surgical technique used. There was no statistically significant impact of any surgical technique on the outcome. Literature suggests greater anatomical success of the IF compared to the complete peeling of ILM. Regarding the functional outcome, the results are more contradictory in the long term.[40,41] In our study, the surgical technique had no impact on either anatomical or functional success. This analysis has the limitations of presenting significantly different absolute number of patients in each group, and it is based on a non-randomized selection of the technique.

The main limitations of this study are the retrospective nature and the performance of PPV by 6 different surgeons. A prospective study with a larger sample should be carried out to confirm which parameters have a greater predictive value in the results of MH surgery. Additionally, aspects such as surgical waiting time and MH size measurements should be standardized across studies.

CONCLUSION

Contrary to previous studies, none of the parameters analyzed proved to have a predictive value for the anatomical surgical success. Regarding the functional result, preoperative BVCA proved to be a factor with a significant impact on surgical success, allowing to predict the visual

results and facilitating the counseling and management of pre-surgical patient expectations.

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