Article

Risk factors for recurrent vitreous hemorrhage in type 2 diabetes patients after posterior vitrectomy.

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Abstract: (Background) the aim was to determine related factors to recurrent vitreous hemorrhage (RVH) in a sample of proliferative diabetic retinopathy (PDR) patients. (Methods) A retrospective, review-based study. We studied 183 eyes from 121 type 2 diabetes patients with PDR. We recorded diabetes duration, history of hypertension, retinal photocoagulation status, the posterior vitreous status, the mean HbA1c, mean hemoglobin, the renal function, and the systemic complications related to diabetes. We also recorded the use of ranibizumab prior to vitrectomy and the following surgical variables: the application of segmentation and diathermy on fibrovascular proliferative tissue, the use of silicone oil, and the occurrence of surgical complications, to study which independent variables were significantly related to the presence of RVH. (Results) Duration of diabetes (P= 0.028), hemoglobin (P=0.02), status of the posterior vitreous (P=0.03), retinal photocoagulation (P=0.002) and use of segmentation surgery technique (P=0.003) have significant link to the presence of RVH. In addition, patients with diabetic polyneuropathy, myocardial infarction and ischemia in lower limbs had more vitreous hemorrhage events (p<0.001). (Conclusions) Patients with PDR and with longer diabetes duration, anemia, attached posterior vitreous, deficient retinal photocoagulation, and previously cardiovascular events, were more prone to RVH.

Keywords: Proliferative diabetic retinopathy, recurrent vitreous hemorrhage, diabetes duration, anemia, posterior vitreous, retinal laser photocoagulation.

1. Introduction

Diabetic retinopathy (DR) is the leading cause of visual loss in the working-age population in developed countries [1]. This is due mainly to ocular complications, such as diabetic macular edema (DME) and vitreous hemorrhage. The latter occurs in patients with proliferative diabetic retinopathy (PDR). The two most established risk factors related to PDR development are diabetes duration [2-4] and the degree of metabolic control of the disease. The Diabetes Control and Complications Trial [5] (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) [6] reported that the poorer the metabolic control the higher the risk of suffering from PDR, in both type 1 (T1DM) and type 2 diabetes patients (T2DM).

There are other systemic risk factors that have been related to the presence and severity of DR in T2DM patients such as blood pressure and diabetic nephropathy. Regarding blood pressure, the UKPDS noted that the risk of PDR development was lower for T2DM patients if blood pressure was controlled [7]. With respect to diabetic nephropathy, different studies have associated the relationship between the ratio of urine albumin to creatinine (UACR) and the estimated glomerular filtration rate (eGFR) with the presence of DR [8]. Along with these well-established risk factors for developing DR, there are others that are less conclusive such as the presence of anemia and chronic obstructive pulmonary disease (COPD). However, some studies found that anemia is a risk

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factor for developing DR in patients with T2DM. In this sense, Bahar et al [9]. found that T2DM patients with anemia were 2.4 times more likely to develop DR and Traveset et al [10] concluded that the level of hemoglobin had a significant inverse association with the severity of DR in T2DM patients. Regarding COPD, some studies have reported a possible relationship with DM. Thus, on one hand Suissa [11] and Dendukuri [12] have pointed to corticosteroids as the agents responsible for the origin and progression of the DM in those patients and on the other hand, other authors have hypothesized that COPD causes T2DM because of inflammatory processes mediated by IL-6 and TNF [13].

The role of anticoagulants and anti-platelets in causing vitreous hemorrhage remains inconclusive. Some authors consider they increase the risk of intraocular hemorrhage while others do not [14, 15].

Regarding the eye, the presence or absence of posterior vitreous detachment (PVD) is probably the most important characteristic in determining the retinal neovascularization in those patients with PDR since the gel acts as a scaffolding for the new vessels to grow, especially in those patients with poor metabolic control [16].

There are two outpatient treatments applied to the eyes with PDR that are known to reduce the risk of retinal hemorrhage, panretinal photocoagulation of the retina (PRP) and intravitreal administration of ranibizumab. Patients with PDR who undergo PRP reduce their vitreous level of VEGF and seem more prone to posterior vitreous detachment (PVD), thus reducing a future risk of vitreous hemorrhage [17]. Regarding ranibizumab, which is a drug with anti-VEGF effect, it is widely used to treat some complications of DR such as DME and PDR. In addition, ranibizumab is used both a few days before the surgery and intraoperatively to minimize the risk of rebleeding.

Those patients with PDR who present with significant vitreous hemorrhage that does not clear on its own, should undergo posterior vitrectomy. In this, the gel is removed and PRP is usually performed to prevent future retinal hemorrhages episodes. In complicated cases where fibrovascular proliferative tissue causes tractional retinal detachment, the bimanual technique is often applied to perform segmentation and delamination to free the retina and prevent the occurrence of retinal tears. In addition, endodiathermy and silicon oil are often used to prevent early rebleeding and allow time for the new vessels to heal [18].

In our experience [19], patients with PDR can be separated into three groups according to their clinical evolution. The first group are patients who never develop vitreous hemorrhage once panretinal photocoagulation (PRP) is carried out. The second group are patients who have had one single episode of vitreous hemorrhage (SVH) in either eye and do not re-bleed after pars plana vitrectomy surgery (PPV) in which the posterior vitreous is completely detached from the retina and retinal laser photocoagulation is usually completed. The third group are patients who develop recurrent vitreous hemorrhage (RVH) in either eye even after vitrectomy, during which the vitreous is detached and the retinal laser photocoagulation is widely applied.

The aim of this study was to evaluate the different risk factors related to RVH episodes in patients with PDR who had previously undergone posterior vitrectomy.

2. Materials and Methods

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2.1. Study design. A We evaluated 183 eyes from 121 T2DM patients (n=126 eyes (65%) from 79 men, n= 57 eyes (35%) from 42 women). All were taken from the reference population of the Hospital Universitari Sant Joan de Reus, Tarragona, Spain. This study is part of our line of research on DR described elsewhere. We conducted a retrospective review of all T2DM patients who had undergone standard three-port pars plana vitrectomy (PPV) for non-clearing vitreous hemorrhage caused by PDR at our hospital.

2.2. Ethical adherence: This study adhered to legal requirements of our local ethics committee (approval CEIM 028/2018) in accordance with the revised guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

2.2. Inclusion criteria. All patients with T2DM, diagnosed with PDR in our health care areas, who presented with vitreous hemorrhage that needed vitreoretinal surgery between 1st June 2010 and 30th June 2020.

2.3. Exclusion criteria. Patients with any previous type of retinal vascular occlusion. Patients with proliferative retinopathy of causes other than diabetes. Patients who had previously been operated on for other retinal conditions.

2.4. Objectives. We aimed to investigate which clinical factors and surgical procedures are related to the presence of recurrent vitreous hemorrhage (RVH) in a population of patients diagnosed with proliferative diabetic retinopathy (PDR) who had undergone 25-gauge posterior vitrectomy.

2.5. Methods.

2-5-1 Clinical and surgical variables studied:

All eyes were assessed by fundus examination, optical coherence tomography (OCT) and fluorescein angiography (FA) to ensure the presence of PDR and to classify the type of DME after the PPV was performed. All eyes underwent ocular ultrasonography to evaluate further details such as objectify the presence of the vitreous attached to the macula or to rule out a tractional retinal detachment.

We conducted a comprehensive review of the electronic health report for all T2DM patients, including age, gender, DM treatment (insulin or oral antidiabetic drugs), DM duration and blood pressure. We recorded the body mass index (BMI), estimated glomerular filtration rate (eGFR), the existence of urine albumin to creatinine ratio (UACR) and the mean HbA1c and hemoglobin levels measured at one year before having been diagnosed with PDR and throughout the study period. We identified the patients treated with anticoagulant or anti-platelet drugs and those diagnosed with chronic obstructive pulmonary disease (COPD). Finally, we identified the patients who had suffered from polyneuropathy, stroke, ischemic cardiopathy or ischemia in the lower limbs.

All eyes were evaluated for the type of DME using the SD-OCT (TOPCON 3D OCT-2000). We classified the patients into three groups:

No DME

Focal or multifocal DME: whether one or multiple areas of exudative microaneurysms were identified along with increased retinal thickness.

Diffuse DME (whether more than 75% of the fluorescein leakage observed was not related to the presence of microaneurysms).

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All eyes were evaluated according to the status of the posterior vitreous using the ultrasonography and/or intraoperatively. All eyes were classified into two subgroups depending on whether the vitreous was initially attached to the posterior pole. In addition, we recorded the patients who had previously been treated with ranibizumab for macular edema. Finally, we recorded those eyes that have previously undergone retinal laser photocoagulation before the first vitrectomy in which we quantified the number of retinal laser sessions applied. A laser session was considered if the number of laser spots was at least 250.

We recorded some intra-surgical variables such as the application of segmentation, delamination, and diathermy on the fibrovascular proliferative tissue of the retina. Also, we recorded the occurrence of retinal tears during each vitrectomy.

We classified all the eyes with PDR into two groups depending on the behaviour of their vitreous hemorrhage. The first group were those with eyes that had bled just once (SVH), and the second group were those with eyes that had bled more than once (RVH). In addition, we further classified them into two subgroups, depending on the time of recurrence. Early recurrence was considered within 15 days after PPV and late recurrence after this period.

The severity of all vitreous hemorrhage episodes was scored on a 5-point scale according to Lieberman et al [20], as follows: grade 0 (no vitreous hemorrhage); grade 1 (minimal vitreous hemorrhage, optic disk and retinal vessels were clearly visible); grade 2 (mild vitreous hemorrhage, most of the optic disk and retinal vessels were visible); grade 3 (moderate vitreous hemorrhage, optic disk or retinal vessels were barely visible); grade 4 (severe vitreous hemorrhage, too dense to allow visualization of the optic disk).

In our study, eyes that showed vitreous hemorrhage of grades 3 or 4 and did not clear after 2 months, underwent PPV along with additional retinal laser photocoagulation.

2.5.2. Surgical technique:

All operations were carried out by four vitreoretinal surgeons who had more than 5 years' experience, under peribulbar anesthesia and using the Bausch&Lomb Stellaris PC (Bausch&Lomb, USA). A wide-angle contact indirect viewing system with a built-in image inverter was used in all cases. All patients underwent 25-gauge standard three-port PPV. In this, the vitreous gel was removed and panretinal laser photocoagulation was performed. In those cases where fibrovascular proliferative tissue caused tractional retinal detachment, the bimanual technique was applied to perform segmentation and delamination to free the retina. In most of these cases, endodiathermy and silicon oil were used to avoid early rebleeding or retinal detachment due to the formation of more than one iatrogenic hole. At the end of the procedure, the cannulas were carefully removed and all the sclerotomies were sutured to avoid postoperative ocular hypotony, and in all cases intravitreal ranibizumab was administered at the end of surgery.

2.6. Statistical analysis.

Data was analysed using the SPSS software package, version 25.0. In this study, the dependent variable was the presence of recurrent vitreous hemorrhage. The independent

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clinical and demographic variables were age, gender, DM duration, type of DM treatment, arterial hypertension, existence of UACR, eGFR, mean HbA1c, mean hemoglobin, the presence of CPOD and treatment with anticoagulant or anti-platelet drugs. The outpatient treatment variables studied were the use of ranibizumab before the first vitrectomy and the number of retinal laser photocoagulation sessions applied in each eye before the first vitrectomy. The independent surgical variables were the application of segmentation and delamination techniques, the use of diathermy, the use of silicon oil as a tamponade, and the occurrence of iatrogenic retinal tears.

A descriptive statistical analysis was made of the quantitative data. For qualitative data, we used the analysis of frequency and percentage in each category. The normal data curve was evaluated using the Kolmogorov-Smirnov test. Differences between quantitative variables with normal distribution were examined using Student's t-test, in other cases we used the Mann-Whitney U test. Inferential analysis for qualitative data was carried out using the chi-squared table and the determination of the Phi test. To correlate two continuous quantitative variables with normal distribution we used Pearson's parametric coefficient. For categorical variables we used Spearman's coefficient. We used the logistic regression analysis to study which independent variables were significantly related to the presence of RVH. We used the multiple regression analysis to study which independent variables were significantly related to the number of vitreous hemorrhage episodes. $P<0.05$ was considered statistically significant.

3. Results

3.1. Diabetes patients with PDR were recruited between 1st June 2010 and 30th June 2020. The majority of participants were men (79/65%) and 42 were women (35%). The

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mean age of the sample was 64.12 ± 12.54 . The mean follow-up period was 8.47 ± 1.17 years (7-21). Table 1 shows the baseline differences between the SVH and RVH groups with respect to clinical data and outpatient treatments received. In the present study, 183 eyes with PDR had vitreous hemorrhage of which 68 eyes (37%) had RVH. The majority of eyes that had RVH re-bled once (61%) and twice (33%). Fifty-seven eyes (84%) had late RVH and 11 eyes (16%) had early RVH.

3.2. Study of clinical risk factors:

Women had a greater proportion of eyes with SVH and men had the same proportion of eyes in both the SVH group and RVH group (p=0.01). However, the gender did not related to the presence of RVH. As shown in Table 1, patients in the RVH group had longer duration of DM compared with the SVH group. Patients who suffered multiple vitreous hemorrhage episodes showed lower levels of hemoglobin, had longer duration of their diabetes and the vitreous attached to the retina. In addition, they had previously undergone fewer retinal laser sessions compared to the others. Regarding systemic diabetic complications, those patients who had greater vitreous hemorrhage episodes were more likely to have suffered ischemia in their lower limbs, ischemic heart disease and diabetic neuropathy.

Table 1. Baseline differences of all independent variables between the 2 groups of patients with proliferative diabetic retinopathy (PDR) studied. UACR= urine albumin to creatinine ratio; eGFR= estimated glomerular filtration rate; COPD=chronic obstructive pulmonary disease; PRP=panretinal photocoagulation; PVD: posterior vitreous detachment. *=Chi-squared test; **=Mann Whitney U test; ***=Student's t test. Phi+= Mathews correlation coefficient. F++= F de Snedecor.

Variable	Single vitreous haemorrhage (SVH)	Recurrent vitreous haemorrhage (RVH)	Significance
Gender: Men Women	 38 (48%) 33 (78%)	 41 (51%) 9 (22%)	Phi^{+}=0.180, p=0.002*
Age (yrs)	66.08 ± 11.81 (28-88)	62.59 ± 15.51 (34-91)	F^{++}=4.131, p=0.017**
DM duration (yrs)	22.02 ± 9.30 (20.3-23.7)	24.35 ± 10.65 (21.7-26.9)	F=2.721, p=0.043**
Arterial hypertension	21 (29.5%)	8 (15.1%)	Phi=0.083, p=0.37*
DM treatment: Insulin Oral drugs	 57 (81%) 14 (19%)	 43 (87%) 7 (13%)	Phi=0.082, p=0.38*
Anticoagulant users	18 (6.3%)	18 (6.3%)	Phi=0.13, p=0.07*
Anti-platelet users	59 (20.7%)	37 (13%)	Phi=0.093, p=0.295*
No Previous PRP Previous PRP	31 (27%) 84 (73%)	37 (54%) 31 (46%)	Phi=-0.275, p=0.005*
No COPD COPD	84 (80%) 31 (20%)	44 (44.7%) 24 (20.3%)	Phi=0.088, p=0.23*
Hemoglobin (g/dL)	12.60 ± 1.55 (12.3-12.8)	11.71 ± 1.89 (11.2-12.1)	F=5.69, p=0.001**

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Mean HbA1c	8.81 ± 1.61 % (8.5-9.1)	8.88 ± 1.77 % (8.4-9.3)	F=0.004, p=0.773***
No UACR UACR	39 (55%) 32 (44%)	22 (45%) 28 (56%)	Phi=0.120, p=0,165*
eGFR (ml/min/1.73^2)	66.25 ± 25.66 (61.51-70.99)	60.63 ± 25.55 (54.71-66.55)	F=0.361, p=0.147**
No PVD PVD	57 (49%) 58 (51%)	50 (73%) 18 (27%)	F=0.02, p=0.001**
Previous therapy Ranibizumab	71 (62%) 43 (38%)	39 (57%) 28 (43%)	Phi=0.049, p=0.804*

Table 2 shows that the longer the duration, the greater number of vitreous hemorrhage episodes (r=0.183; p=0.013), The duration of diabetes, the level of hemoglobin, the number of laser retinal sessions, the presence of the posterior vitreous attached to the retina, and the performance of retinal tissue segmentation and delamination maneuvers were the risk factors in our population of diabetic patients with proliferative diabetic retinopathy that showed recurrent vitreous hemorrhage (Figure 1).

Table 2. Study of each independent variable in relation to the recurrence of vitreous hemorrhage, assessed by means of logistic regression analysis. eGFR= estimated glomerular filtration rate; COPD=chronic obstructive pulmonary disease; VEGF=vascular endothelial growth factor; PRP=panretinal photocoagulation; PVD: posterior vitreous detachment.

Independent Variables	**Exp(B)**	**CI 95%**	**Significance***
Gender	-0.004	-0.231-0.228	p=0.31
Age	-0.221	-0.023-(-0.004)	p=0.09
DM duration	1.39	0.01-0.024	p=0.028
Body Mass Index	0,726	-0.022-0.15	p=0.44
Arterial hypertension	1.73	0.78-3.84	p=0.17
DM treatment	-0.058	-0.343-0.111	p=0.31
Anticoagulant therapy	0.265	-0.046-0.494	p=0.11
Antiplatelet therapy	0.259	0.010-0.392	p=0.48
Number of retinal laser sessions	0.631	0.470-0.847	p=0.002
COPD	-0.023	-0.285-0.196	p=0.65
Hemoglobin	748	0.626-0.893	p=0.001
HbA1c	0.905	-0.061-0.049	p=0.82
UACR	0.885	0.45-1.73	p=0.72
eGFR	-0.087	-0.007-0.002	p=0.21
Previous Anti-VEGF therapy	0.010	-0.157-0.188	p=0.47
Posterior Vitreous Detachment	2.261	1.198-4.265	p=0.012
Segmentation / Delamination	0.60	0.023-0.157	p<0.0005
Use of silicon oil	0.23	0.215-0.776	p=0.001
Diathermy	1.02	0.998-1.061	p=0.06
Retinal tear	1.03	0.987-1.073	p=0.09

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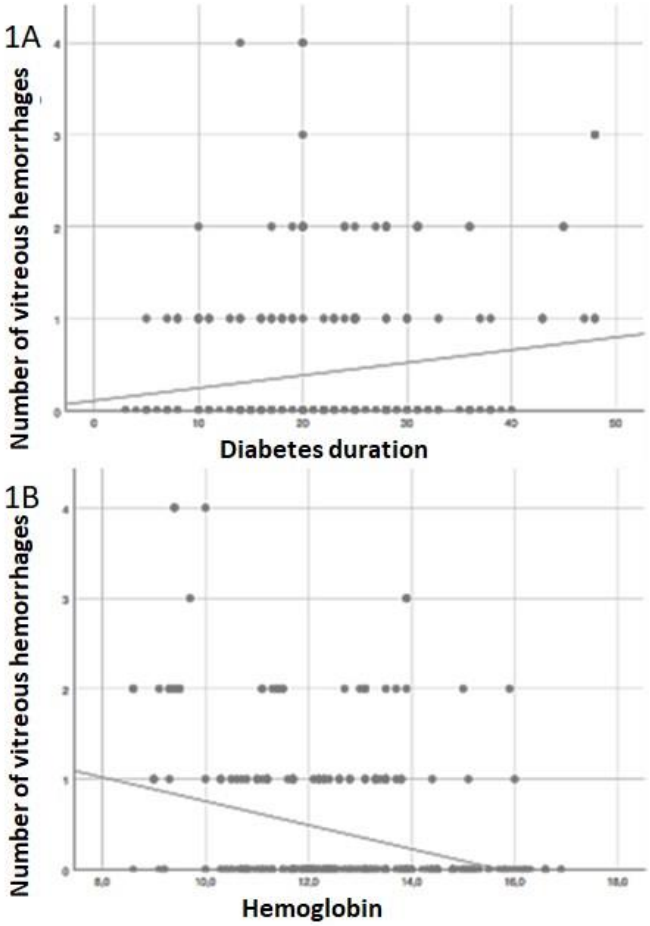
Figure 1. Number of vitreous hemorrhage events as a function of the diabetes duration and the level of hemoglobin. (1A) Scatter plot that shows a positive correlation between the duration of diabetes and the number of vitreous hemorrhage events. (1B) Scatter plot that shows a negative correlation between the hemoglobin level and the number of vitreous hemorrhage episodes.



The mean of hemoglobin was different between groups: SVH = 12.60 ± 1.55 and RVH = 11.71 ± 1.89 (p=0,001). The lower the hemoglobin level the more episodes of vitreous hemorrhage (r= - 0.306; p<0.001) (Table 2) (Figure 1).

Regarding the status of the vitreous, significant differences were found between the groups of patients at the beginning of the study (p=0.001). In total, 107 eyes (59%) had the vitreous attached to the retina initially whereas 76 eyes (41%) showed PVD. Patients in the former group were younger (59.41 ± 12.78) than those with PVD (72.34 ± 10.19). In the RVH group, most eyes had the vitreous initially attached to the retina while in the SVH group, it was only observed in half of the eyes. The vitreous attached to the posterior pole of the eye was found to be a risk factor for RVH (OR= 2.26, 95% CI,1.198-4.265, P= 0.012) (Table 2).

Patients diagnosed with COPD were distributed homogeneously across both groups so it was not linked to vitreous re-bleeding. Patients on anti-platelet or anticoagulant treatment were distributed homogeneously across both groups and did not show an increased risk of presenting eye re-bleeding.

In the present study, the mean of HbA1c was similar in the two groups of patients and we did not observe a correlation between the level of HbA1c and the number of vitreous hemorrhage events.

Regarding the type of treatment, patients treated with oral antidiabetic drugs (17%) or with insulin (83%) were similar and it did not suggest any tendency to present re-bleeding. The BMI was

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similar at the start of the study and did not correlate with any tendency to present vitreous hemorrhage. Regarding both the UACR and the eGFR, there were no differences between the groups at the start of the study and did not suggest any significant tendency to suffer with RVH.

3.3. Relationship with other diabetes complications:

The existence of systemic complications was recorded in all patients. Approximately one third of patients (38%) with diabetic polineuropathy developed RVH, which is a higher percentage than the others ($p<0.001$). Similarly, those patients diagnosed with some type of ischemia in lower limbs (35%) were more prone to RVH when compared to the others ($p<0.001$). In the same way, those patients who had ischemic cardiopathy (25%) were more prone to RVH ($p<0,001$). The rate of occurrence of stroke was similar among groups and did not relate with eye re-bleeding.

3.4. Diabetic macular edema:

We evaluated the presence and type of DME in both groups of eyes with PDR at the start of the study. In the SVH group, 31 eyes (27%) did not have DME, 52 eyes (45.2%) had focal DME and 32 eyes (27.8%) had diffuse DME. In the RVH group, 12 eyes (17.6%) did not present with DME, 17 eyes (25%) had focal DME and 39 eyes (57.4%) had diffuse DME. Therefore, eyes with RVH presented with diffuse DME at a significantly greater percentage than the others ($p<0.001$).

3.5. Study of outpatient retinal treatments:

We evaluated the effect of retinal laser photocoagulation and intravitreal ranibizumab, both applied before the first vitrectomy, in the prevention of recurrent vitreous hemorrhages.

3.6. Study of the effect of retinal laser photocoagulation:

Sixty-eight eyes included in the study did not receive retinal laser treatment prior to vitrectomy. On the other hand, 24, 42, 31, 14, and 4 eyes underwent 1, 2, 3, 4, and 5 laser retinal sessions, respectively. Eighty-four eyes of the SVH group had received at least one laser session (46%) and only 31eyes (17%) of the RVH group. Therefore, those eyes that had been previously treated with laser before the first surgery were less likely to bleed again ($p<0.0005$) (Table 2).

3.7. Study of the effect of ranibizumab:

Forty-three eyes in the SVH group (60%) and 28 eyes (40%) in the RVH group had previously received ranibizumab for DME. Most eyes had received 3 injections (37.5%). Seventy-one eyes (65%) in the SVH group and 39 eyes in the RVH group were not previously treated with ranibizumab. The previous treatment with ranibizumab therapy, independently of the number of injections, did not influence the tendency to re-bleeding ($P=0.80$).

3.8. Study of surgical procedures:

We recorded the differences observed with respect to the application of segmentation and delamination maneuvers, the use of endodiathermy and silicon oil, and the occurrence of iatrogenic retinal tears in the two groups of patients studied (Table 3).

Table 3. Differences in surgical variables between the 2 groups of patients studied with proliferative diabetic retinopathy. *=Chi-squared test.

Variable	SVH	RVH	Significance
Segmentation / Delamination			
Yes	5 (4%)	43 (63%)	Phi=0.647, p=0.005*
No	110 (96%)	25 (37%)	

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Endodiathermy			
Yes	25 (22%)	23 (34%)	Phi=0.133, p=0.07*
No	90 (78%)	45 (66%)	
Silicon oil			
Yes	15 (13%)	27 (40%)	Phi=0.306, p=0.005*
No	100 (87%)	41 (60%)	
Occurrence of retinal tears			
Yes	3 (3%)	36 (57%)	Phi=0.594, p=0.005*
No	112 (97%)	32 (43%)	

3.9. Study of the effect of segmentation and delamination:

Forty-three eyes (63%) in the RVH group and only 5 eyes (4%) in the SVH group underwent segmentation and delamination surgical maneuvers (P<0.0005). In addition, segmentation and delamination were significantly related to the presence of multiple vitreous hemorrhage events (P<0.0005).

3.10. Study of the effect of diathermy:

Diathermy was applied to 25 eyes (22%) in the SVH group and 23 eyes (33%) in the RVH group (P=0.07). This maneuver did not significantly related to the presence of multiple vitreous hemorrhage events (P=0.08).

3.11. Study of the effect of silicon oil:

In 42 eyes (23%) silicon oil had been used as a tamponade at the end of surgery: 29 eyes (69%) re-bled while 13 eyes (31%) did not. One hundred forty-one eyes had not received silicon oil and only 44 re-bled (31%). Significantly more eyes that had received silicon oil re-bled (p=0.001).

3.12. Study of the occurrence of retinal tears during vitrectomy:

Thirty-six eyes (53%) in the RVH group had at least a retinal tear during vitrectomy and only 3 eyes (2.6%) in the SVH group (P<0.0005). However, the occurrence of retinal tears was not considered a surgical risk factor for the presence of recurrent vitreous hemorrhage events.

3.13. Causes of eye rebleeding:

Eleven eyes showed early RVH. In ten eyes the eye re-bleeding was objectified within the first 24 hours, of which the intraocular pressure was inferior to 10 mmHg in seven eyes (64%). In all the cases, an active residual fibrovascular membrane was observed. Fifty-seven eyes presented with late RVH. In thirty-five eyes (61%) we observed recurrent neovascular membrane formation on the posterior pole, in 13 eyes (23%) fibrovascular ingrowth was observed at the sclerotomy sites through doppler ultrasonography, and in 9 eyes (16%) we could not establish the cause of the ocular re-bleeding.

4. Discussion

The present study focused on the changes in DR screening during the COVID-19 pandemic in our HCA. The study shows a reduction in the number of patients attending during 2020 (Table 3). However, Figure 1 shows that fewer patients attended during March and April 2020, and numbers subsequently reduced a little each time there was a new wave of COVID-19. Screening numbers recovered in 2021 and again in the first half of 2022. In the year 2021 we have observed that 17.97% were patients scheduled for the

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year 2020 who did not attend their appointment, but a greater number of DR was not observed in these patients.

This study included a significantly greater number of men and in population-based studies of prevalence other authors found a greater proportion of men with severe PDR. Klein et al [21]. found that men were twice as likely to suffer from PDR as women in southern Wisconsin whereas Nittala et al [22] reported that being male together with duration of diabetes were the strongest risk factors for the development of PDR in a Latin-American population. Furthermore, Hammes et al. reported that being male was a risk factor for developing TDM2 in a large prospective study in Central Europe [23].

In the present study, we observed that patients with RVH had a significantly lower blood hemoglobin level. Qiao et al [24] and Bahar et al [25] research groups found that DM patients with hemoglobin levels lower than 12 mg/dl were twice as likely to develop DR. In addition, Yafeng et al. found that anemia, independently of diabetic nephropathy, seems to play a significant role in the progression of DR to more severe forms [26]. It seems logical, therefore, to suppose that patients with PDR with lower hemoglobin levels aggravate their retinal hypoxia, which could then lead to a greater formation of new vessels. The etiology and pathogenesis of anemia in DM patients is multifactorial. Chronic hyperglycemia causes oxidative stress, autonomic neuropathy and sympathetic denervation, leading to renal hypoxia and finally a reduction in the erythropoietin production [27].

Patients with a longer duration of their DM were more prone to suffer RVH. It is well known that duration of diabetes is probably the strongest predictor for development and progression of DR [28]. The longer the duration of the diabetes the more likely it is to develop inflammatory factors, such as platelet derived growth factor and VEGF, which have an active role in the evolution of DR and the development of new vessels [29].

Arterial hypertension is a well-established risk factor for the progression of DR in T2DM patients. The UKPDS reported that the better the blood pressure control in T2DM patients, the lower the risk for developing PDR [7]. Half of participants of each group in our study were diagnosed with high blood pressure and as a result, we found no differences between them.

In the present study, the majority of eyes in the RVH group had the vitreous initially attached to the retina compared to the SVH group, which only had half of the eyes with the vitreous attached. Although the posterior hyaloid was removed in the first vitreoretinal surgery in those eyes that bled, the likelihood of peripheral vitreous remnants being attached to the retina, along with the retinal ischemia, might facilitate the growth of new vessels and the occurrence of subsequent episodes of vitreous hemorrhage in some eyes.

The type of DME reported in the two group of patients was quite different. The most common type of DME in the SVH group was focal DME whereas in the RVH group it was the diffuse DME. Those eyes with higher level of VEGF were possibly more prone to both a higher level of growth of new vessels and an alteration of the inner blood retinal barrier, leading to RVH and diffuse DME.

Patients in our study with RVH had more myocardial and lower limb ischemia compared to the SVH group. However, the incidence of stroke was similar among them. Xiao-Rong et al [30]. found a graded relationship between the severity of DR and the risk of all-cause mortality in patients with T2DM, mainly due to heart failure and stroke, which is indicative that PDR individuals have more risk factors than those with non-proliferative DR. Similarly, in a prospective cohort study, Cheung et al [31] found that DR was an independent risk factor for ischemic stroke [32]. Other studies are

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inconclusive however about the association between DR and stroke. The UKPDS [6] reported that DR was not a significant risk factor for stroke and the Wisconsin Epidemiological Study of Diabetic Retinopathy concluded that only PDR was associated with stroke in T2DM patients, not NPDR [33]. Unlike non-diabetic patients, the type of stroke in diabetic patients mainly affects microvascular circulation instead of large vessels [34].

In our study, those eyes that had previously undergone retinal laser photocoagulation had fewer vitreous hemorrhage events. The greater the number of retinal sessions applied to the eyes, the fewer episodes of vitreous hemorrhage they presented. Patients with PDR who undergo PRP reduce their vitreous level of VEGF, thus reducing a future risk of vitreous hemorrhage [17]. On the other hand, we observed that the tendency to rebleed was similar regardless of whether the eyes had been treated with ranibizumab or not. Treated eyes received only a mean of 3 ranibizumab injections, which could explain the lack of anti-VEGF effect observed.

Forty-eight eyes (26%) underwent segmentation and delamination by bimanual surgery, which represented a large proportion of the total. Our reference diabetic population is mostly of rural origin, and a significant proportion of patients usually go to the ophthalmology service once DR becomes noticeable. For this reason, it is very common to visit patients with multiple fibrovascular proliferations in both eyes who have not previously received retinal laser photocoagulation. Forty-three eyes (89%) that underwent segmentation and delamination suffered RVH. Intra-surgical diathermy was used in half of the cases that required segmentation and delamination and only in 17% of those that did not. Although this procedure helped us to prevent the majority of eyes from bleeding intraoperatively, it did not significantly reduce the tendency to rebleed in the long term. Silicon oil was used as a tamponade in 42 eyes (23%) of which 27 (64%) experienced late RVH. Those eyes to which silicon oil was administered as a tamponade at the end of the PPV were more likely to re-bleed compared to the others after its removal. We think the reason might be that silicon oil is reserved for the most complicated eyes and although no eye re-bled while being on silicon oil, some did after it was removed.

We objectified intraoperatively the occurrence of at least one retinal tear in 39 eyes (21%) of which 38 were being treated by segmentation and delamination.

The most frequent causes observed of rebleeding were persistent or recurrent neovascular membrane formation (57 eyes, 78%) on the posterior pole and fibrovascular ingrowth at the sclerotomy sites (13 eyes, 18%).

To our knowledge this is the first study aimed at evaluating clinical, epidemiological and surgical differences between patients with PDR whose eyes do not bleed once the posterior vitrectomy is carried out and in whom PRP is usually completed compared with those patients who tend to re-bleed despite undergoing vitrectomy and retinal laser photocoagulation. The limitations of our study are its retrospective design and the small sample size.

In the present study, we observed that both clinical and surgical variables were related to the presence of multiple vitreous hemorrhage events.

5. Conclusions.

Our study found that the patients with PDR who are the most prone to eye re-bleeding are men who have a longer duration of their diabetes, have anemia, have the vitreous attached to the retina, did not undergo retinal laser photoagulation and have previously suffered a cardiovascular event. In addition, those complicated eyes in which it was necessary to apply segmentation and delamination maneuvers and the use of silicon oil,

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also had a greater tendency to re-bleed. Therefore, treatment of anemia and early application of retinal laser photocoagulation is recommended to reduce the likelihood of re-bleeding.

List of abbreviations

RVH: recurrent vitreous hemorrhage
PDR: proliferative diabetic retinopathy
BMI: body mass index
UACR: urine albumin to creatinine ratio
eGFR: estimated glomerular filtration rate
DR: diabetic retinopathy
DM: diabetes mellitus
DME: diabetic macular edema
DCCT: Diabetes Control and Complications Trial
UKPDS: United Kingdom Prospective Diabetes Study
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus
PRP: panretinal photocoagulation
PVD: posterior vitreous detachment
SVH: single vitreous hemorrhage
PPV: pars plana vitreoretinal surgery
OCT: optical coherence tomography
FA: fluorescein angiography
COPD: chronic obstructive pulmonary disease
VEGF: vascular endothelial growth factor

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Authors' contributions:

(MBB) contributed to study conception and design, collected research data, reviewed the statistical analysis, wrote the discussion and edited the manuscript, contributing to the final approval of the version sent for publication. (PRA) contributed to ophthalmology data collection, carried out retinography and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication. (AMP) contributed to ophthalmology data collection, carried out fluorescein angiographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication. (ABP) contributed to ophthalmology data collection, carried out retinography and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication. (IRB) contributed to ophthalmology data collection, carried out fluorescein angiographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication. (MVJ) contributed to medical history data collection, carried out OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication. (RNG) contributed to ophthalmology data collection, carried out retinography and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication. (MLLS) contributed to ophthalmology data collection, carried out fluorescein angiographs and OCT procedures and interpreted the research data, contributing to the final approval of the version sent for publication.

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