

# Multiple factors in the prediction of risk of recurrent vitreous haemorrhage after sutureless vitrectomy for non-clearing vitreous haemorrhage in patients with diabetic retinopathy

YUHUA DING

JIANGSU PROVINCE HOSPITAL

BANGTAO YAO

LISHUI DISTRICT PEOPLE'S HOSPITAL

HUI HANG

JIANGSU PROVINCE HOSPITAL

HUI YE (✉ [yehui\\_njmu@163.com](mailto:yehui_njmu@163.com))

JIANGSU PROVINCE HOSPITAL

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## Research article

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# Abstract

## Background

We aimed to analyse multiple factors in the prediction of risk of postoperative recurrent vitreous haemorrhage (RVH) for non-clearing vitreous haemorrhage in patients with diabetic retinopathy (DR) who underwent sutureless vitrectomy with 23- (23G) or 25-gauge (25G) narrow-gauge systems.

## Methods

A retrospective consecutive case series design was used. DR patients who underwent sutureless vitrectomy for non-clearing vitreous haemorrhage between June 2017 and October 2019 were enrolled. All operations were performed at a tertiary hospital. Patient demographics and risk factors, including age, gender, duration of diabetes, preoperative fasting blood sugar levels (FBSL), systolic blood pressure (SBP), serum creatinine (Cr), urea, triamcinolone acetonide (TA), electrical coagulation, air-fluid exchange, pan-retinal photocoagulation status (PRP), anti-vascular endothelial growth factor drug (anti-VEGF), and other factors, were recorded. Patients were divided into two groups based on the timing of their postoperative RVH: immediate postoperative RVH (within 2 weeks after operation) and delayed postoperative RVH (beyond 2–4 weeks after operation).

## Results

Overall, 167 eyes (167 patients) were enrolled. Seventy eyes were underwent 23G and 25G sutureless vitrectomy performed in 97 eyes, respectively. Postoperative RVH developed in 18 eyes (25.7%) in Group 23G and in 20 eyes (21.6%) in Group 25G ( $P = 0.540$ ). Of these, 3 eyes (4.3%) had severe RVH in Group 23G compared with 5 eyes (5.2%) in Group 25G ( $P = 0.584$ ). Delayed postoperative RVH occurred in 6 eyes (8.6%) in Group 23G and 8 eyes (8.2%) in Group 25G ( $P = 0.789$ ). A binomial logistic regression analysis revealed that age, duration of diabetes, and Cr level were significantly associated with RVH in both Group 23G ( $P < 0.05$ ) and Group 25G ( $P < 0.05$ ).

## Conclusions

The incidence and severity of RVH were 25.7% and 4.3%, respectively, in Group 23G and 21.6% and 5.15%, respectively, in Group 25G. Thus, the 23G sutureless vitrectomy approach was as safe as the 25G sutureless vitrectomy approach for treating vitreous haemorrhage in patients with DR. A younger age, shorter duration of diabetes, and higher Cr levels were risk factors for postoperative RVH in sutureless vitrectomy.

## Background

Diabetes mellitus (DM) is a common chronic metabolic disease with an increasing prevalence worldwide—more than half a billion individuals are projected to have DM by 2030 [1, 2]. Furthermore, diabetic

retinopathy (DR) is the most common microvascular complication of DM and is responsible for up to 4.8% of blindness globally [3]. Despite the use of anti-vascular endothelial growth factor (anti-VEGF) drugs or laser for the treatment of diabetic macular oedema and proliferative DR (PDR) [4, 5, 6], vitrectomy surgery remains necessary in up to one-third of eyes with DR [7]. Vitreous haemorrhage (VH) is one of the most common PDR complications and the main cause for sudden vision loss in PDR patients [8]. Non-clearing VH (NCVH) is a good indicator of pars plana vitrectomy (PPV), with vision improvements reported in approximately 75% of PDR patients after diabetic vitrectomy [9]. However, one of the most common postoperative complications associated with NCVH is recurrent vitreous haemorrhage (RVH), which may cause visual impairments and require reoperation [10].

The incidence rate of RVH in PDR patients has been reported to range from 11.8–75% [11, 12]. Early studies have found that the most common causes of RVH after vitrectomy are fibrovascular ingrowth at the sclerotomy sites, residual or recurrent neovascular membrane formation on the retina, and insufficient retinal photocoagulation [13, 14].

In the present study, we focused on a series of patients with DR who were undergoing sutureless 23G or 25G vitrectomy for NCVH. We aimed to analyse the incidence and possible risk factors for RVH following sutureless 23G and 25G vitrectomies.

## Methods

A retrospective consecutive case series design was used. Patients undergoing sutureless vitrectomies for NCVH between June 2017 and October 2019 at a tertiary hospital (The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital) were enrolled. We excluded cases with a history of previous scleral buckling, PPV, other coexisting ocular disorders such as glaucoma and uveitis, use of sutures for the incisions, silicone oil or inert gas injection during the operation.

A variety of pre-, intra-, and postoperative patient characteristics were assessed. Characteristics included patient age, gender, duration of DM, visual acuity, intraocular pressure (IOP), anterior and posterior segment findings, a history of pan-retinal photocoagulation (PRP), the date of surgery, and any subsequent visits were recorded. Preoperative test results such as fasting blood sugar levels (FBSL), systolic blood pressure (SBP), serum creatinine (Cr), blood urea, prothrombin time (PT), activated partial thromboplastin time (APTT), and prothrombin standardisation ratio (PT-INR) were also recorded. Surgical characteristics including usage of triamcinolone acetonide (TA), electrical coagulation, air-fluid exchange, pre-PRP, and anti-VEGF use were determined from the patient's operative record. All patients were followed-up routinely at 1 day, 1 week, 2 weeks, 4 weeks, 2 months, 3 months, and 6 months post-operation. Depending on the commencement of RVH, patients were divided into immediate postoperative RVH (within 2 weeks after operation) and delayed postoperative RVH (beyond 2–4 after operation) groups. In addition, the severity of postoperative RVH was classified as follows: grade 0 (no haemorrhage), grade 1 (mild-to-moderate: optic disc, macula, and retinal vessel visibility), or grade 2 (severe: retina details were not seen).

All operations were performed by subspecialist vitreoretinal consultants who had more than 10 years of experience. All operations were performed under peribulbar anaesthesia and using the Alcon Constellation

23G or 25G systems (Alcon, Geneva, Switzerland). A wide-angle non-contact indirect viewing system with a built-in image inverter was used in all cases. All patients underwent standard three-port PPV with a combination of dissection and removal of the fibrovascular membranes and vitreoretinal traction. TA staining, electrical coagulation for active bleeding during the operation, air-fluid exchange, and extensive laser photocoagulation surgery were performed as required. No intraocular tamponade (silicone oil or inert gas) was used. At the end of the procedure, cannulas were carefully removed without suturing. Phacoemulsification surgery was performed to remove the clouded lens, which affected the vitrectomy, and an artificial lens was implanted when required. Preoperative anti-VEGF therapy was used in selected patients with informed consent given their extent of neovascularisation. This study followed the tenets of the Declaration of Helsinki. Approval from the appropriate ethics committee was obtained, and informed consent was acquired from all patients before surgery.

## Statistical analyses

All analyses were performed using SPSS version 23.0 for Windows. Descriptive statistics were determined. To compare the two groups, univariate analyses using Chi-squared test or T-test were performed, as appropriate. Binomial logistic regression analyses were also performed. A two-sided p-value < 0.05 was considered statistically significant.

## Results

In total, 167 eyes from 167 DM patients with UCVH met the inclusion criteria during the 31-month study period. These included 103 male and 64 female patients with a mean age of 52.9 years (range 26–81). From these patients, 70 eyes underwent 23G sutureless PPV and 97 eyes underwent 25G sutureless PPV.

The clinical characteristics and operation-related variables of the participants are shown in Table 1. Clinical characteristics, including gender, age, preoperative SBP, preoperative FBSL, serum Cr, urea and pre-PRP agents, did not differ significantly between Groups 23G and 25G. Duration of DM was shorter in Group 23G than in Group 25G (10 years vs 12 years). In particular, PT, APTT, PT-INR, pre- and postoperative IOP in all patients were in a normal range and as such were excluded from subsequent analyses. The two groups differed in operation-related characteristics such as TA usage, elector-al-coagulation usage, air-fluid exchange, and anti-VEGF drug usage.

Table 1  
Clinical characteristics and operation-related variables of the study participants

Characteristics	23G	25G	p-value
Eyes, n	70	97	
Male, n(%)	43(61.4)	60(61.9)	0.955
Age, years(mean ± SD)	54.70 ± 11.31	51.63 ± 12.74	0.109
Preoperative systolic blood pressure,mmHg(mean ± SD)	138.01 ± 18.42	136.13 ± 20.17	0.539
Diabetes			
Duration, years	10.00(5.00–15.00)	12.00(6.50–16.50)	0.041
Preoperative fasting blood glucose level, mmol/L	5.62(4.70–7.41)	5.96(5.05–7.19)	0.639
Serum creatinine, µmol/L	77.55(58.78–104.93)	76.00(59.15–127.00)	0.359
Urea, mmol/L	6.51(5.41–8.88)	6.67(4.81–8.90)	0.502
Triamcinolone acetonide usage, n(%)	63(90.0)	59(60.8)	< 0.001
Elctral-coagulation usage, n(%)	12(17.1)	7(7.2)	0.046
Air-fluid exchange, n(%)	66(94.3)	66(68.0)	< 0.001
Pre-panretinal photocoagulation, n(%)	12(17.1)	15(15.5)	0.771
Anti-vascular endothelial growth drug usage, n(%)	10(14.3)	33(34.0)	0.004

A 6-month follow-up was achieved in all patients from both groups. The incidence and severity of RVH across groups is shown in Table 2. The incidences of postoperative RVH were 25.7% and 21.6% in Groups 23G and 25G, respectively. There were no significant differences between the two groups ( $p = 0.540$ ). There were 3(4.3%) and 5(5.15%) severe postoperative RVH cases (Grade 2) in Groups 23G and 25G, respectively, which ultimately required additional surgeries (e.g., vitreous lavage or PPV). There were no significant differences in postoperative RVH severity between the two groups ( $p = 0.584$ ). Delayed RVH occurred in 6 eyes ((8.6%) in Group 23G and in 8 eyes (8.2%) in Group 25G ( $p = 0.789$ ) (Table 3).

Table 2  
Incidence rate and severity of RVH

	<b>23G</b>	<b>25G</b>	<b>p-value</b>
Incidence rate			
RVH, n(%)	18(25.7)	21(21.6)	0.540
No RVH, n(%)	52(74.3)	76(78.4)	
Grade			
Grade 0, n(%)	52(74.3)	76(78.35)	0.584
Grade 1, n(%)	15(21.4)	16(16.5)	
Grade 2, n(%)	3(4.3)	5(5.15)	

Table 3  
Immediate RVH and delayed RVH

	<b>23G</b>	<b>25G</b>	<b>p-value</b>
Immediate RVH, n	12	13	0.789
Delayed RVH, n	6	8	
No RVH, n	52	76	

The analysis of the individuals with or without postoperative RVH is shown in Table 4. Patient age ( $p = 0.006$ ,  $p < 0.001$ ), duration of DM ( $p = 0.007$ ,  $p = 0.003$ ), and serum Cr ( $p = 0.002$ ,  $p = 0.009$ ) were significantly different between participants with and without postoperative RVH in both Groups 23G and 25G. Additionally, the level of urea ( $p = 0.005$ ) was significantly different between participants with and without postoperative RVH in Group 25G. A binomial logistic regression analysis revealed risk factors of postoperative RVH (Table 5). Age ( $p = 0.019$ ,  $p = 0.004$ ), duration of DM ( $p = 0.046$ ,  $p = 0.02$ ), and serum Cr levels ( $p = 0.006$ ,  $p = 0.042$ ) were significantly different between participants with and without postoperative RVH in both Groups 23G and 25G.

Table 4  
 Characteristics of individuals with or without postoperative RVH

	<b>23G(n = 70)</b>			<b>25G(n = 97)</b>		
	No RVH(n = 52)	RVH(n = 18)	p-value	No RVH(n = 76)	RVH(n = 21)	p-value
Sex(male/female)	31(59.6)	12(66.7)	0.596	46(60.5)	14(66.7)	0.608
Age, years(mean ± SD)	56.94 ± 10.45	48.22 ± 11.46	0.006	53.96 ± 11.85	43.19 ± 12.52	< 0.001
Duration of diabetes, years	10.00(5.00–17.00)	5.00(3.00–9.25)	0.007	12.50(8.50–17.00)	6.00(2.00–15.00)	0.003
Preoperative fasting blood glucose level, mmol/L	5.88(4.88–7.44)	5.27(3.99–6.97)	0.149	5.93(5.09–7.06)	6.04(4.21–7.97)	0.646
Preoperative systolic blood Pressure,mmHg	137.60(100–183)	139.22(92–187)	0.702	135.03(88–190)	140.14(100–187)	0.464
Serum creatinine, µmol/L	70.40(53.33–88.78)	108.80(66.78–231.28)	0.002	71.80(56.08–118.00)	95.00(68.80–373.60)	0.009
Urea, mmol/L	6.47(5.17–7.58)	8.14(5.42–13.36)	0.066	5.88(4.79–7.81)	9.40(5.49–14.04)	0.005
Triamcinolone acetonide usage, n(%)	48(92.3)	15(83.3)	0.523	45(59.2)	14(66.7)	0.536
Elctral-coagulation usage, n(%)	10(19.2)	2(11.1)	0.671	6(7.9)	1(4.8)	0.988
Air-fluid exchange, n(%)	49(94.2)	17(94.4)	1.000	52(68.4)	14(66.7)	0.879
Pre-panretinal photocoagulation, n(%)	9(17.3)	3(16.7)	1	14(18.4)	1(4.8)	0.233
Anti-vascular endothelial growth drug usage, n(%)	9(17.3)	1(5.6)	0.402	25(32.9)	8(38.1)	0.656

Table 5  
Results of binomial logistic regression analysis for risk factors of postoperative RVH

	23G		25G	
	OR(95%CI)	p-value	OR(95%CI)	p-value
Sex(male/female)	0.237(0.027-2.10)	0.196	0.399(0.55–2.874)	0.399
Age, years	0.894(0.814–0.982)	0.019	0.888(0.819–0.963)	0.004
Duration of diabetes, years	0.833(0.697–0.997)	0.046	0.835(0.716–0.972)	0.02
Preoperative fasting Blood glucose level	0.928(0.628–1.371)	0.708	1.182(0.851–1.640)	0.319
Preoperative systolic Blood pressure	1.019(0.969–1.072)	0.467	0.993(0.948–1.041)	0.783
Serum creatinine, $\mu\text{mol/L}$	1.028(1.008–1.049)	0.006	1.009(1.000–1.019)	0.042
Blood urea	0.986(0.929–1.046)	0.637	1.226(0.968–1.553)	0.09
Triamcinolone acetonide usage	1.597(.146-17.503)	0.701	0.265(0.036–1.952)	0.265
Elctral-coagulation usage	0.906(0.047–17.634)	0.948	5.358(0.160–179.699)	0.349
Air-fluid exchange	6.411(0.187–219.818)	0.303	1.166(0.169–8.065)	0.876
Pre-panretinal photocoagulation	11.994(0.372–386.950)	0.161	9.206(0.655–129.45)	0.1
Anti-vascular endothelial growth drug usage	0.426(0.040–4.530)	0.479	2.193(0.358–13.438)	0.396

## Discussion

With the rapid development of surgical techniques and instruments, the incidence of postoperative RVH in PDR has fallen significantly from 75% in the 1980s to approximately 11.8–40% [11, 12, 15, 16]. Khuthaila et al. reported an incidence rate of 32% for postoperative RVH with 23G PPV in PDR patients [17], while Mahallngam et al. reported an RVH incidence of 21.6% [18]. Similarly, in the present study, the incidences of postoperative RVH were 25.7% and 21.6% in Groups 23G and 25G, respectively.

Research is ongoing to elucidate the risk factors of postoperative RVH. Mahallngam et al. and Tolentino et al. reported that a younger patient age was significantly associated with postoperative RVH [18, 19]. In the present study also, the age influenced postoperative RVH. There are two possible explanations for this; one

related to surgery and the other with patients themselves. First, it more difficult to induce a complete posterior vitreous detachment in younger patients than the older ones because of their stronger vitreoretinal adhesions. When a residual split posterior vitreous cortex remains firmly attached to the retina, it serves as a natural scaffold for the proliferation of neovascularisation membrane. Vitreous contraction and subsequent traction on unhealthy fibrovascular membranes can induce postoperative re-bleeding. A second explanation for the impact of patient age on postoperative RVH is that the onset of PDR in younger patients indicates a more rapid disease progression and thus, more aggressive disease. In some cases, this also indicates a broader area of active neovascularisation. Given this, the increasing numbers of unhealthy neovascular vessels bleed easily.

The present study also identified the duration of DM as a predictor of increased postoperative RVH risk. Epidemiologic data reveals that PDR almost never develops within the first 10 years of DM onset [20]. A possible explanation for this is that some patients lack an awareness of their DM and their disease may develop for many years without any diagnosis or treatment. Given this, a shorter duration of DM at the time of presentation may reflect the patient's ignorance of the disease, leaving it uncontrolled for many years. In patients with a longer duration of DM, treatment might have been used more consistently and for a longer period; therefore, their degree of PDR may be less severe. Therefore, we contend that the clinicians should pay more attention to the patients with a shorter DM onset time (and thus later detection).

In the present study, we reported for the first time that Cr was a novel RVH risk predictor and strongly associated with postoperative RVH. Cr is the most common index used for renal function. Compensatory kidney function is very powerful. The Cr values won't be increased, unless the degree of kidney damage accounts for more than half of the kidney. Higher Cr values in the present study represented poor renal function and a poor general state of health due to poor control of pre-operation blood sugar levels. Kussman et al. reported that in the typical clinical course of diabetic nephropathy, the mean duration of DM at the onset of early renal function failure was approximately 19 years [21]. The higher the Cr value, the longer the duration of DM. Combined with the risk predictor of postoperative RVH mentioned above, a shorter duration of DM at the time of presentation, which confirms again that the disease had been ignored and uncontrolled for many years. Given this, the patients with higher Cr values in the present study may have had more aggressive PDR, thus increasing their risk of postoperative RVH.

As has previously been found, silicone oil and inert gases such as SF<sub>6</sub> and C<sub>3</sub>F<sub>8</sub> may decrease the incidence of postoperative RVH, especially in early RVH cases [22]. One possible reason for this may be that longstanding mechanical tamponade of fragile retinal vessels by oil or gas bubbles that occurs with this procedure. This tamponade also concentrates coagulation factors within the close proximity of bleeding sites, thereby promoting the re-establishment of vascular integrity. We, therefore, excluded cases from the present study in which silicone oil or inert gas tamponade appeared to minimise any interference by these factors and to isolate other predictors of postoperative RVH risk.

After the first commercially available narrow-gauge vitrectomy system was described by Fujii et al. in 2002, a high number of narrow-gauge systems were employed worldwide [23]. These revolutionary advances led to faster postoperative recovery, less postoperative discomfort, reduced surgically-induced astigmatism,

and a quicker entry and exit from the eye [24]. Furthermore, 23G devices retained the fluid dynamics and instrumental rigidity offered by 20G systems and required minimal changes in the surgical technique. The 25G system further improved fluidics and rigidity. Owing to these advantages, both two narrow-gauge systems are often used by the surgeons. Thus, in the present study, patients with DR who underwent both sutureless 23G and 25G PPV for NCVH were included. While the incisions created during 25G PPV do not require sutures, 23G PPV incisions sometimes do. As such, we only included the patients who underwent sutureless 23G PPV in the present study to eliminate any influence associated with the sutures.

One of the disadvantages of the sutureless technique is hypotony. It remains unclear whether hypotony is significantly correlated with postoperative RVH; however, both the advantages and disadvantages have been reported previously in the literature [12, 25]. In the present study, both pre- and postoperative IOP were within the normal range. Thus, any relationship between the hypotony and postoperative RVH was not assessed in this study.

The present study has a few limitations. One was the number of patients who used anti-VEGF drugs. Due to the high cost of anti-VEGF drugs, few people can afford this treatment and thus, a few patients included in this study used them. Therefore, in the present study, the relationship between anti-VEGF drug use and postoperative RVH remains unclear. A larger sample size is needed to explore this aspect more closely. Another limitation was that there were few cases of delayed or severe postoperative RVH among the participants of the present study. Hence, we were unable to investigate the risk factors associated with delayed and severe postoperative RVH. Third, only preoperative FBSL were recorded. A high level of preoperative FBS only reflected the difficulty of glycemic control during a short period, and can be influenced by many facts including perioperative stress. Further studies are required to clarify the relationship between perioperative hyperglycemia and postoperative complications.

## Conclusions

The incidence and severity of RVH were 25.7% and 4.3%, respectively, in Group 23G and 21.6% and 5.2%, respectively, in Group 25G. The findings of our study suggest that 23G sutureless vitrectomy was as safe as 25G sutureless vitrectomy for NCVH in patients with DR. The practical applications of the study to clinical domains and public policy deserved attention. A younger age, shorter duration of DM, and higher Cr levels were significant predictors of postoperative RVH risk in patients who underwent sutureless vitrectomy.

## Abbreviations

23G or 25G

23- or 25-gauge narrow-gauge

APTT

Activated partial thromboplastin time

Cr

Creatinine

DM

Diabetes mellitus  
DR  
Diabetic retinopathy  
FBSL  
Fasting blood sugar level  
IOP  
Intraocular pressure  
NCVH  
Non-clearing vitreous haemorrhage  
PDR  
Proliferative diabetic retinopathy  
PPV  
Pars plana vitrectomy  
PRP  
Pan-retinal photocoagulation  
PT  
Prothrombin time  
PT-INR  
Prothrombin standardisation ratio  
RVH  
Recurrent vitreous haemorrhage  
SBP  
Systolic blood pressure  
TA  
Triamcinolone acetonide  
VEGF  
Vascular endothelial growth factor  
VH  
Vitreous haemorrhage

## **Declarations**

### **Ethics approval and consent to participate**

The study followed the tenets of the Declaration of Helsinki. Approval was obtained from the ethics committee of Jiangsu Province Hospital.

### **Consent for publication**

Informed written consent had been obtained from the patient.

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

YHD collected the data of the patient, consulted literatures and wrote the manuscript; BTY edited the manuscript, analyzed the data and dealt with the tables; HH gave useful suggestions on writing and improved the manuscript; HY contributed design of study and approved the submitted version. YHD and BTY contributed equally to this article, they are co-first authors of the article. All authors read and approved the final manuscript.

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