• Clinical Research •

Predictive lipidaemic and clinical factors for PVR formation after RRD surgery in nondiabetic patients

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Abstract

● **AIM:** To investigate the potential impact of lipidaemic and clinical factors on the development of proliferative vitreoretinopathy (PVR) following uncomplicated primary rhegmatogenous retinal detachment (RRD) surgery in nondiabetic individuals.

● **METHODS:** This was a retrospective, single-center, case-control study of consecutive patients who underwent primary RRD surgery. The study group comprised 145 patients who developed PVR within 3y of follow-up, while the control group comprised 161 patients with RRD who did not develop PVR. Cox regression analysis was utilized to identify independent associations between various risk markers and the occurrence of PVR.

● **RESULTS:** The mean age of patients was 52.31y (SD=13.29), and 54.25% (*n*=166) were male. The median time to PVR formation after surgery was 150d. Multivariate Cox regression indicated that cigarette smoking status [hazard ratio (HR): 0.43, 95% confidence interval (CI): 0.31-0.60, *P*<0.001], retinal detachment (RD) not involving the macula (HR: 0.52, 95%CI: 0.37-0.73, *P*<0.001), apolipoprotein A1 (ApoA1; HR: 1.01, 95%CI: 1.01-1.02, *P*<0.001) and apolipoprotein E (ApoE; HR: 3.81, 95%CI: 1.64-8.85, *P*=0.002) were independent predictors of PVR.

● **CONCLUSION:** Apart from macular involvement and smoking, the lipidaemic factors ApoA1 and ApoE are risk factors of PVR after primary RRD surgery.

● **KEYWORDS:** apolipoprotein A1; apolipoprotein E; nondiabetic patients; prognostic nomogram; proliferative vitreoretinopathy; rhegmatogenous retinal detachment; vitrectomy

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INTRODUCTION

Proliferative vitreoretinopathy (PVR) is a scarring condition that can occur together with retinal detachment (RD) or after initial RD repair surgery[1-2]. The pathogenesis of PVR development is characterized by an immediate complex biochemical and cellular reaction that has been divided into three overlapping phases: inflammation, cellular migration and proliferation and then membrane formation[3-5]. PVR is typified by the emergence of epiretinal and subretinal contracting membranes and is the primary cause of surgical failure in rhegmatogenous RD (RRD)[6]. The incidence of PVR in all RD cases is estimated to be between 5% and 11%[7-8].

The findings regarding predictive risk factors are inconsistent on the occurrence of PVR after RD repair at present[1,8-10]. Risk factors such as smoking, involvement of the macular region in RD, baseline PVR, blood neutrophil-to-lymphocyte ratio, trauma and giant retinal tears (RT) have been identified as being associated with an elevated incidence of PVR[1,11-14]. In prior research, a correlation was established between serum lipoprotein levels and a heightened susceptibility to proliferative diabetic retinopathy (PDR) where PVR existed[15]. Additionally, a separate investigation discovered an elevation in apoprotein A1 levels in the vitreous of severe PVR patients when compared to those with moderate PVR[16]. Previous related studies have shown a correlation between PVR and lipid metabolism. Lipid metabolites can lead to the development of

PVR by aggravating the inflammatory response[17-18]. A recent study found that the use of statin treatment, which regulates the serum lipidaemic level, lowered the risk of revitrectomy in patients operated on due to RRD by 28%[19]. In addition, related studies have also confirmed that the anti-inflammatory effects of apolipoprotein A1 (ApoA1) and apolipoprotein E (ApoE) play a role in a variety of diseases[20-23]. Taken together, these studies suggest the potential utility of serum lipidaemic levels in predicting the development of PVR.

Despite these findings, the relationship between serum lipidaemic profiles and PVR formation remains underexplored, particularly in nondiabetic patients where the confounding effects of diabetes-related metabolic changes are absent. Given the growing evidence implicating lipid metabolism in retinal pathologies, investigating lipidaemic factors in PVR development could uncover novel predictive biomarkers and therapeutic targets.

This study aims to address this knowledge gap by evaluating the association between serum lipidaemic levels and PVR formation following primary RRD surgery in nondiabetic patients. By integrating lipidaemic data with established clinical risk factors, we seek to identify a comprehensive set of predictive factors that can enhance risk assessment, guide clinical decision-making, and potentially inform future preventive strategies for PVR.

PARTICIPANTS AND METHODS

Ethical Approval This case-control study followed the guidelines stated in the Declaration of Helsinki and obtained approval from the Institutional Ethics Review Board of Shanghai General Hospital (No.K-2023-186). Furthermore, the research adhered to the regulations set forth by the Health Insurance Portability and Accountability Act (HIPAA). Each patient provided written informed consent.

Study Design This study randomly selected patients with RRD who received RD repair surgery at Shanghai General Hospital from January 2016 to December 2019 and had 3y of follow-up records after surgery. The patients who were enrolled in the study were stratified into two groups: a PVR group, which consisted of individuals who had developed PVR after surgery during 3y of follow-up, and a control group, which comprised patients who did not exhibit PVR formation after surgery. All individuals who met the eligibility requirements were contacted and informed about the goals of our study, following which they voluntarily participated in the study without any supplementary remuneration.

Inclusion and Exclusion Criteria The study involved a meticulous review of patient charts and operative reports, with a focus on cases featuring primary RRD surgery. In instances where both eyes were affected, only the one with worse primary visual acuity was considered. The diagnosis of RRD was determined by observing detached retinas caused by concurrent retinal breaks clinically. Similarly, the diagnosis of PVR was confirmed through slit-lamp examination, direct and indirect ophthalmoscopy, and fundus images in accordance with the classification system established by the Silicone Study Group[24]. Patients were enrolled in the study if they met the following key inclusion criteria: 1) 18y and older, regardless of gender; 2) clinical manifestations of RRD; 3) ability to sign a written informed consent and comply with study assessments for the duration of the study. The study employed exclusion criteria consisting of the following: 1) a medical history of diabetes or fasting blood glucose levels equal to or greater than 6.7 mmol/L; 2) giant RT encompassing one or more quadrants; 3) macular hole; 4) prior vitreoretinal surgery for any reason; 5) tractional or recurrent RD; 6) RD resulting from trauma, penetrating injury, or endophthalmitis; 7) intraoperative complications during primary RD repair, such as suprachoroidal haemorrhage; 8) incomplete collection of data for major parameters.

Patient Records All participants underwent routine preoperative and postoperative evaluations. To reduce or eliminate any possible bias in case selection, the cases were matched by ages and genders. The surgeons were granted autonomy to select the surgical procedure [either pars plana vitrectomy (PPV) or scleral buckle (SB)] and tamponade agent (either sterilized air or silicone oil) of their preference. The Alcon Constellation system (Alcon Laboratories, Inc., Fort Worth, TX, USA) was used by surgeons to operate 23-gauge PPV to these patients. Following the PPV procedure, patients were required to visit the surgeon's clinic for follow-up appointments at intervals of 1, 2wk, 1mo, and every 2mo for a period of one year, followed by annual visits for the next 2y. In the event of rapid vision loss, phototherapy or floaters, or peripheral vision loss, patients were instructed to seek immediate medical attention if symptoms worsened.

The clinical and surgical notes documented various ophthalmic examinations for each patient, including best-corrected visual acuity (BCVA; *via* Snellen chart) and intraocular pressure (IOP; through noncontact tonometry). These examinations were conducted to identify findings consistent with PVR. Specifically, PVR cases in follow-up visits were defined as patients presenting with proliferative epiretinal membrane formation resulting in RD, causing diffuse contraction of the posterior retina with or without subretinal membranes and necessitating additional surgery.

Data Collection Preoperative variables encompassed a range of factors[14], including age, gender, smoking history, alcohol consumption, high blood pressure status (defined in the patient medical reports), hypertension status (as defined in the patient's medical records), BCVA, IOP, status of myopia, including

high myopia [defined as refractive error equal to or greater than 6.0 diopters (D)] and mild/moderate myopia (defined as refractive error ranging from -6.0 to 0 D), lens condition, retinal break location, retinal break number, presence of macula involvement in RD, lattice degeneration (LD), posterior vitreous detachment (PVD), vitreous haemorrhage (VH; defined as confirmed VH based on the Collaborative Ocular Melanoma Study), and duration of symptoms (*e.g.* floaters, photopsias or peripheral vision loss) related to RD (defined as the time between RRD symptoms and primary RRD surgery). The study examined various serum lipidaemic factors by automatic biochemical analyser (Beckman Coulter AU5800, USA), including triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), small dense low-density lipoprotein (sdLDL) cholesterol, ApoA1, ApoE, apolipoprotein B (ApoB), apolipoprotein A2 (ApoA2), apolipoprotein C2 (ApoC2), and lipoprotein (a). Among them, triglycerides and total cholesterol were measured by enzymatic method. ApoA1, ApoA2, ApoB, ApoC2 and ApoE were measured by immunoturbidimetric method. HDL and LDL were measured by kits (direct method). Lipoprotein (a) was measured by latx-enhanced immunoturbidimetric method. SdLDL was measured by catalase method. Additionally, intraoperative variables such as surgical technique (PPV or SB) and tamponade agent (sterilized air or silicone oil) were also investigated.

Statistical Analysis The computations were analysed with SPSS (version 21.0, IBM Corp, New York, NY, USA) and R (version 4.2.3). LogMAR units of 2.1, 2.4, and 2.7 were allocated to the assessment of finger counting, hand movement, and light recognition, respectively[25]. Variables with categorical data are presented as frequency (percentage), while variables with continuous data are presented as mean [standard deviation (SD)]. PVR formation duration following a primary RRD surgery is measured by median [interquartile range (IQR)]. The demographic and clinical characteristics were compared using different statistical tests: Student's *t*-test was used for continuous factors with a normal distribution, the nonparametric Mann-Whitney *U* test for continuous factors with a skewed distribution, and the Chi-squared test (or Fisher's exact test, if appropriate) for categorical factors. To identify the factors contributing to PVR formation while accounting for possible confounding variables, Cox regression methods were applied. The reported hazard ratio (HR) included its corresponding 95% confidence interval (CI). All tests were two-sided. A statistically significant result was considered to be a *P* value less than 0.05. Results of Cox regression were used to establish a nomogram to determine the rates of developing PVR at 1-year and 3-year intervals. C-index was used to assess the model's recognition ability. To evaluate the concordance between the predicted and observed results, the calibration curves of the nomogram were analysed for the rates at 1 and 3y.

RESULTS

This study comprised 306 patients who underwent primary RRD surgery, of whom 145 had PVR formation and 161 did not. The mean age of patients was 52.31y (SD=13.29), and 54.25% (*n*=166) were male. The average duration of follow-up was 710d with an SD of 452d and the median time for PVR formation after primary RRD surgery was 150d (IQR, 90-365d). After primary RRD surgery, PVR formation occurred in 113 eyes (77.93%) with one year and thirty-two eyes (22.07%) after 1y.

Table 1 presented the demographic characteristics of the PVR group and control group. The two groups did not differ statistically significantly in any of the following terms: age, gender, duration of symptoms, alcohol consumption, high blood pressure, myopia status, BCVA and IOP. However, it is noteworthy that a significantly higher proportion of patients with PVR formation had a history of cigarette smoking (46.90% *vs* 18.63%, *P*<0.001).

The majority of patients (92.8%, *n*=284) underwent primary RRD surgery using PPV, as opposed to SB (7.2%, *n*=22). Silicone oil was the most frequently utilized tamponade agent (80.4%, *n*=227) for primary repair. Table 1 also showed the preoperative related serum lipidaemic details as compared between the PVR and control groups. Neither group showed any further differences with respect to triglycerides, total cholesterol, HDL, sdLDL, ApoA1, ApoE, ApoB, ApoA2, ApoC2, or lipoprotein (a). The mean ApoE level at the baseline visit was significantly higher in individuals who developed PVR than in those who did not (0.85±0.20 *vs* 0.76±0.19 mg/L, *P*<0.001), and other factors included LDL (3.01±0.82 *vs* 2.80±0.76 mmol/L, *P*=0.021) and ApoA1 (44.43±23.89 *vs* 35.48±15.77 g/L, *P*<0.001). The comparison of preoperative and operative details between the different groups is also presented in Table 2. Both groups did not differ significantly in any of the following aspects: retinal break location, retinal break number, lens status, LD of the operated eye, presence of VH, PVD, tamponade agent, or technique. The main difference between the PVR and control groups was the proportion of RD involving the macula (59.31% *vs* 33.54%, *P*<0.001).

Univariate analysis revealed that individuals who did not smoke had a 0.41 times lower HR (95%CI, 0.30-0.57; *P*<0.001) for PVR formation than those who were current or former smokers (Table 3). Additionally, RD not involving the macula had a 0.46 times lower HR (95%CI, 0.33-0.65; *P*<0.001) for PVR formation. Other preoperative factors, including LDL, ApoA1, and ApoE, were also found to be associated with PVR formation following primary RRD

Table 1 Demographic information between PVR group and control group (*n*=306) mean±SD, *n* (%)

Characteristics	PVR group (*n*=145)	Control group (*n*=161)
Age (y)	51.91±15.70	52.66±10.70
≤50	59 (40.69)	59 (36.65)
>50	86 (59.31)	102 (63.35)
Gender		
Male	82 (56.55)	84 (52.17)
Female	63 (43.45)	77 (47.83)
Duration of symptoms (d)	18.17±13.83	17.29±18.84
≤14	99 (68.28)	123 (76.40)
>14	46 (31.72)	38 (23.60)
Cigarette smoking status[a]		
Never	77 (53.10)	131 (81.37)
Previous or current	68 (46.90)	30 (18.63)
Alcohol drinking status		
Never	57 (39.31)	50 (31.06)
Previous or current	88 (60.69)	111 (68.94)
HBP status		
Yes	23 (15.86)	33 (20.50)
No	122 (84.14)	128 (79.50)
Myopia		
High myopia	31 (21.38)	33 (20.50)
Moderate/mild myopia	5 (3.45)	9 (5.59)
None	109 (75.17)	119 (73.91)
BCVA (logMAR)	1.34±0.51	1.32±0.56
IOP (mm Hg)	13.36±3.09	13.35±2.33
Follow-up duration (d)[a]	299±332.05	1080±0
≤365	113 (77.93)	0
>365	32 (22.07)	161 (100)
Triglycerides (mmol/L)	5.06±1.04	4.96±0.96
Total cholesterol (mmol/L)	1.34±0.28	1.31±0.20
HDL (mmol/L)	1.18±0.34	1.24±0.30
LDL[a] (mmol/L)	3.01±0.82	2.80±0.76
sdLDL (mg/dL)	34.56±14.56	33.50±13.89
Apolipoprotein A1[a] (g /L)	44.43±23.89	35.48±15.77
Apolipoprotein E[a] (mg/L)	0.85±0.20	0.76±0.19
Apolipoprotein B (g/L)	2±1.34	1.75±2.48
Apolipoprotein A2 (mg/dL)	25.69±6.91	25.40±6.54
Apolipoprotein C2 (mg/dL)	5.86±5.72	5.14±3.08
Lipoprotein (a) (mg/L)	182.07±230.16	211.86±210.93

[a]*P*<0.05 between two groups. PVR: Proliferative vitreoretinopathy; SD: Standard deviation; HBP: High blood pressure; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; HDL: High-density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; sdLDL: Small dense low-density lipoprotein cholesterol.

surgery (Table 3). In the multivariate analysis (Table 3), patients who were nonsmokers were 0.43 times (95%CI, 0.31-0.60; *P*<0.001) less likely to have PVR formation than current or former smokers. RD without macula involvement were 0.52 times (95%CI, 0.37-0.73; *P*<0.001) less likely to have occurred

Table 2 Baseline preoperative and operative related characteristics (*n*=306) *n* (%)

Characteristic	PVR group (*n*=145)	Control group (*n*=161)
Preoperative factors		
RD involving macula[a]		
Yes	86 (59.31)	54 (33.54)
No	59 (40.69)	107 (66.46)
Location of retinal break (s)		
Superior half	94 (64.83)	118 (73.29)
Inferior half	42 (28.97)	24 (14.91)
Both	9 (6.21)	19 (11.80)
No. of retinal break (s)		
1	97 (66.90)	101 (62.73)
>2	48 (33.10)	60 (37.27)
Lens status		
Phakic	63 (43.45)	74 (45.96)
Pseudophakic	82 (56.55)	87 (54.04)
Lattice degeneration		
Yes	35 (24.14)	43 (26.71)
No	110 (75.86)	118 (73.29)
Vitreous hemorrhage		
Yes	21 (14.48)	23 (14.29)
No	124 (85.52)	138 (85.71)
Posterior vitreous detachment		
Yes	115 (79.31)	138 (85.71)
No	30 (20.69)	23 (14.29)
Operative factors		
Tamponade agent		
Silicone oil	100 (76.33)	127 (83.00)
Sterilized air	31 (23.66)	26 (20.47)
Technique		
PPV	131 (90.34)	153 (95.03)
SB	14 (9.66)	8 (4.97)

[a]*P*<0.05 between two groups. PPV: Pars plana vitrectomy; PVR: Proliferative vitreoretinopathy; RD: Retinal detachment; SB: Scleral buckle; SD: Standard deviation.

than those with macula involvement. Furthermore, ApoA1 (*P*<0.001) and ApoE (*P*=0.002) were also potential risk factors for PVR formation.

The prognostic nomogram was constructed by integrating all independent predictors for survival related to PVR (Figure 1A). A C-index of 0.577 indicates agreement between the predicted and observed survival probabilities for this model. This model's bias-corrected C-index was 0.555 after bootstrap validations, suggesting moderate discrimination. With increasing prognostic scores, the probability of follow-up completion over 1 and 3y decreased (Figure 1B and 1C). The calibration plots revealed that the predicted completion rates at the 1-year (Figure 2A) and 3-year (Figure 2B) follow-ups were quite consistent with the actual observations. By using the Cox method, patients were categorized into low, intermediate, and high risks groups. Figure 3 illustrated significant differences in PVR-related survival between risk groups (*P*<0.001 for the overall estimate, *P*<0.001 for the low and intermediate

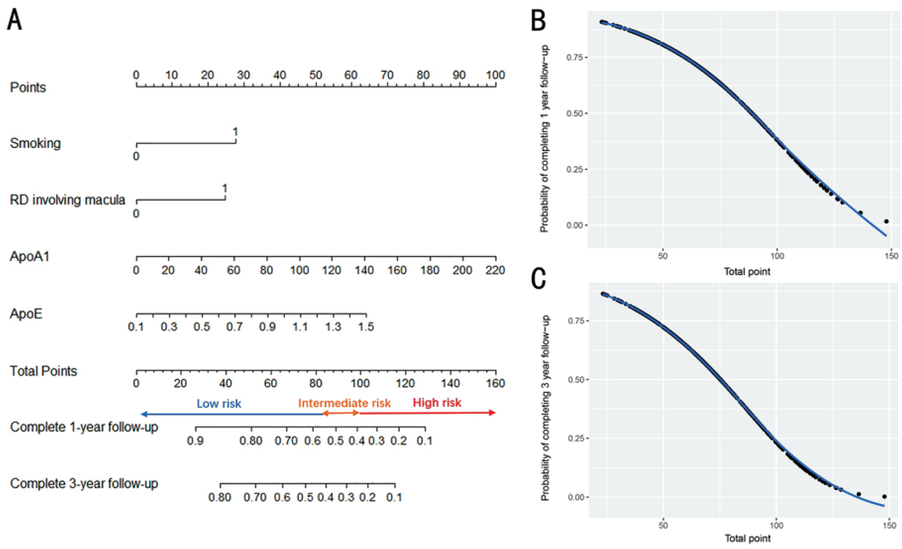

Figure 1 Nomogram for probability of participants completing follow-up A: Nomogram for predicting the probability of participants completing 1 or 3y follow-up. Locate pagetoid spread and draw a vertical line up to the "Points" axis to obtain the score of pagetoid spread for 4 variables: smoking (no/yes), RD involving macula (no/yes), ApoA1 (g/L) and ApoE (mg/L). Scores were then summed and the total number was located on the line labeled "Total Points". The follow-up completion probability is determined at the intersection of 1-year and 3-year follow-up probability axes. B, C: The probability of participants completing follow-up of 1y (B) and 3y (C) is predicted using nomogram scores. ApoA1: Apolipoprotein A1; ApoE: Apolipoprotein E; RD: Retinal detachment.

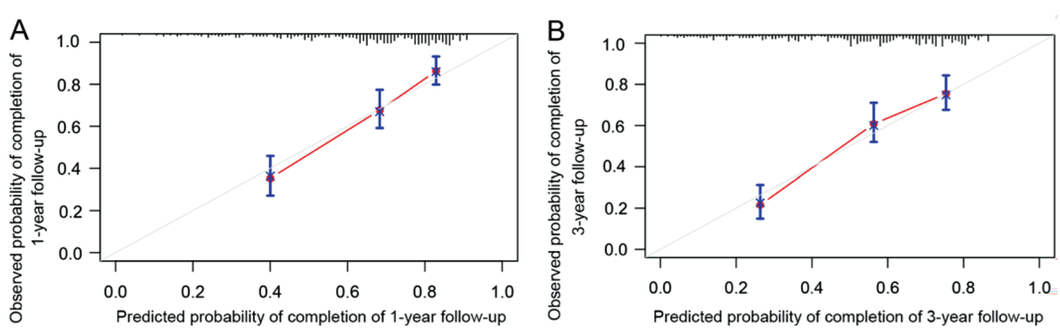

Figure 2 An illustration of the calibration plots for follow-up completion probability at 1y (A) and 3y (B) An x-axis plots nomogram-predicted probability, and a y-axis plots observed probability. Vertical lines indicate 95% confidence intervals of the estimates. An origin-to-destination model with gray lines symbolizing perfect calibration is characterized by predicted probabilities that match actual probabilities. Red dots indicate predicted probabilities; Blue crosses indicate bootstrap corrected estimates. B=1000 repetitions.

Table 3 Analyses of the predictors of PVR using univariate and multivariate cox proportional hazards regression

Items	Univariable		Multivariable	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Cigarette smoking status (never *vs* previous or current smoking)[a]	0.41 (0.30-0.57)	<0.001	0.43 (0.31-0.60)	<0.001
RD involving macular (no *vs* yes)[a]	0.46 (0.33-0.65)	<0.001	0.52 (0.37-0.73)	<0.001
LDL	1.25 (1.02-1.53)	0.030		
Apolipoprotein A1[a]	1.01 (1.01-1.02)	<0.001	1.01 (1.01-1.02)	<0.001
Apolipoprotein E[a]	5.25 (2.29-12.06)	<0.001	3.81 (1.64-8.85)	0.002

[a]Characteristics included in multivariable model. CI: Confidence interval; HR: Hazard Ratio; LDL: Low density lipoprotein cholesterol; RD: Retinal detachment; PVR: Proliferative vitreoretinopathy.

risks, and *P*=0.001 for the intermediate and high risks). The distributions of the risk scores, completion time, completion status, and expression patterns of the four factors are illustrated in Figure 4.

DISCUSSION

PVR is a prevalent cause of unsuccessful RD repair, resulting in the requirement for supplementary surgical intervention and poorer visual outcomes. The literature presents incongruous

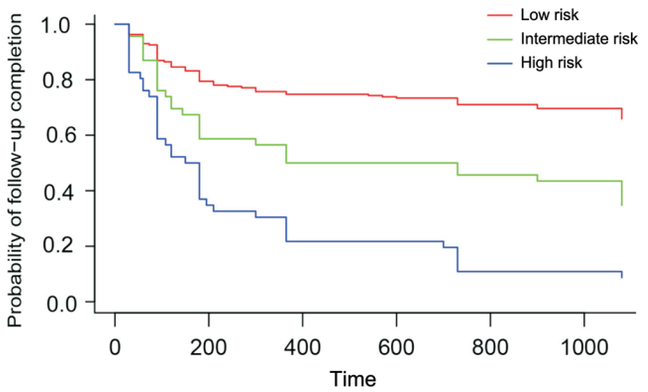

Figure 3 Kaplan-Meier curves of follow-up completion probability for three risk level groups (low, moderate, and high risk) sorted by nomogram score.

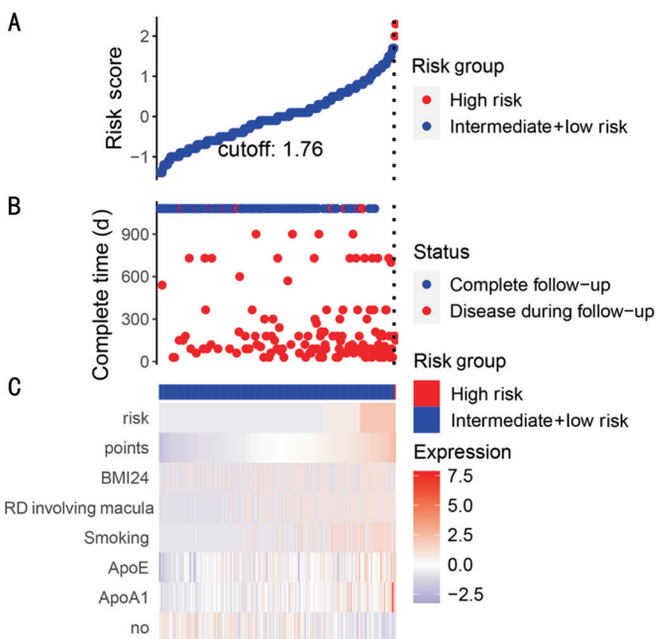

Figure 4 The risk score distribution, completion status distribution, and expression profiles distribution of four factors
ApoE: Apolipoprotein E; ApoA1: Apolipoprotein A1; RD: Retinal detachment; BMI: Body mass index.

and diverse studies regarding the risk factors of PVR, including uveitis, giant RT, aphakia, and high myopia, which remain a topic of debate. In this study, we aimed to identify serum lipidaemic factors that can predict the formation of PVR in cases after RRD surgery. To our knowledge, this is the first evaluation of the predictive factors for PVR formation to involve analysis of preoperative serum lipidaemic and clinical factors among nondiabetic patients who have undergone primary RRD surgery.

The clinico-pathologic findings suggest that PVR is an extension of the physiologic wound-healing response to RRD. Previous studies show that exposure of human fibroblasts to vitreous fluids from patients with PVR causes a rapid and sustained increase in arachidonic acid metabolite release as measured by competitive enzyme-immunoassay. The findings implicate that bioactive lipids, such as prostaglandin E2, is a contributor to enhanced intraocular fibrosis in PVR[17,26]. Many studies have shown that lipid factors are involved in the occurrence and development of a variety of retinal diseases[27-29]. The essence is that blood lipids are involved in the regulation of inflammatory response, including ApoA1 and ApoE[30].

This study demonstrated that baseline serum concentrations of ApoA1 were significantly elevated in patients with PVR compared to a control group. Furthermore, ApoA1 was identified as a potential predictor of PVR formation following primary RRD surgery. The underlying mechanism for this association may involve cytokines that are evaluated during the early stages of PVR development, which facilitate T-cell recruitment and activate mTOR signalling, as indicated by pathway analysis[31]. ApoA1, a primary structural component of HDL[32], plays a key role in retinal lipid metabolism. It facilitates the transport and clearance of lipids within the retina, notably by removing harmful oxidized lipids that accumulate during retinal stress or injury[33]. Beyond its lipid-modulating functions, ApoA1 exerts immunomodulatory effects, including the regulation of the effector T-cell (Teff) to regulatory T-cell (Treg) balance and the suppression of pro-inflammatory cytokine production[34]. Therefore, elevated serum ApoA1 levels might serve as an indicator of the intensity of the inflammatory response in RD, reflecting an adaptive or compensatory mechanism to mitigate tissue damage. This hypothesis is further supported by prior studies that patients with severe PVR exhibit significantly higher ApoA1 concentrations in the vitreous compared to those with mild PVR. These findings suggest a direct correlation between ApoA1 levels and the progression of PVR, potentially driven by localized inflammation and lipid dysregulation in the retinal microenvironment[16]. Collectively, these data underscore the dual role of ApoA1 as both a functional mediator and a biomarker in the development of PVR, offering new avenues for understanding its pathophysiology and improving risk stratification following RRD surgery.

Notably, patients who developed PVR exhibited significantly elevated levels of serum ApoE, highlighting its potential role in the disease process. Statistical analysis further identified ApoE as a significant risk factor, with a striking 3.81-fold increase in serum concentration observed in the PVR group compared to control group. Histopathological examination provided additional insights, revealing the accumulation of neutral lipids and ApoE within the Bruch's membrane, alongside the infiltration of immune cells beneath the retinal pigment epithelium (RPE) layer. These deposits were particularly pronounced in areas characterized by RPE atrophy and thin subretinal lesions, suggesting a localized pathological

process tied to lipid dysregulation and inflammation[35]. Researchers in a previous study also reported higher levels of ApoE in patients with age-related macular degeneration, a condition similarly marked by outer retinal and RPE damage[36]. In the development of PVR, elevated ApoE may also serve as a biomarker of injury to the outer retina and RPE, reflecting the degenerative changes that accompany RD and subsequent fibrotic complications. Intriguingly, ApoE4, one of three common ApoE variants (ApoE2, ApoE3, and ApoE4), has been implicated in modulating inflammatory and neuroprotective responses in other ocular models. For instance, studies in glaucoma have shown that ApoE4 inhibits neurodegenerative microglial activation and confers protection against retinal ganglion cells (RGCs) loss[37], contrasting with the pro-inflammatory tendencies of other isoforms. This raises the possibility that elevated ApoE4 levels in PVR might represent a compensatory anti-inflammatory or neuroprotective mechanism triggered by RD, aimed at mitigating further tissue damage. However, the precise role of ApoE, and particularly ApoE4, in PVR pathogenesis remains incompletely understood. The interplay between ApoE accumulation, lipid metabolism, and immune cell activity in the subretinal space warrants further investigation. Future studies should explore whether ApoE isoforms differentially influence PVR progression and whether targeting ApoE-related pathways could offer therapeutic benefits in preventing or managing PVR following RD repair.

Cigarette smoking is anticipated to predict the development of PVR following a primary RRD surgery, aligning with previous studies[14]. The precise aetiology of this correlation remains elusive. However, the extant literature suggests that PVR formation is linked to the breakdown of the blood–retinal barrier[8] and recent experimentation in a murine model has demonstrated that cigarette smoking can undermine the stability of this barrier[38]. Additionally, smoking is known to elicit an inflammatory response in developing retinal tissues[39]. This mechanism speeds up the movement and growth of retinal pigment epithelial cells that are discharged into the vitreous after RD. Further investigation is needed to elucidate the correlation between smoking and the occurrence of uveitis and retinal neovascularization, which may bear resemblance to this phenomenon[40-41]. Moreover, additional studies are required to determine the influence of cigarette smoking on the formation of PVR following RRD surgery.

With respect to preoperative anatomy, our study revealed that macula-involving RDs exhibited a higher propensity for the development of PVR than macula-sparing RD. Prior research has established a robust correlation between the extent of RD and PVR[1,10]. The pattern of macula involvement is probably a substitute for duration and an indicator of the extent of RD, both increase the likelihood of PVR development[42]. Consequently, we recommend that referring and treating doctors prioritize the timely repair of detachments that spare the macula as a preventive strategy to avoid PVR formation in cases where the macula is involved.

The literature lacks a comprehensive investigation into the duration of PVR formation following primary RRD surgery. The average duration for PVR formation ranges from 19 to 501d[14]. In our study, 63.4% developed PVR within 6mo after primary RRD surgery, with a median duration of 145d for PVR formation. Our study differed from previous research in that we utilized silicone oil in a greater number of cases. Prior investigations have indicated that air tamponade may elevate the risk of PVR formation when compared to alternative tamponade agents (silicone oil)[8]. This may be attributed to the transient tamponade effect of air, which may not adequately promote wound healing and may ultimately lead to PVR formation following RD repair. As such, it is advisable to closely monitor patients for potential sequelae during both the early and late postoperative periods.

Our research is distinctive as it incorporates lipidaemic baseline characteristics in both the case and control groups, rendering the findings practical and relevant to real-world patients. However, the study is constrained by its retrospective design, which may have introduced confounding variables despite our efforts to mitigate them, as evidenced by the C-index of 0.555, which indicates moderate discrimination ability of the nomogram. Although the nomogram may not be a standalone predictive tool, it provides valuable insights for risk stratification when combined with clinical judgment. To comprehensively comprehend risk factors of developing PVR following primary RRD surgery, a larger sample cohort study and the inclusion of additional biomarkers are needed. Besides, our study has another limitation. Since this study is a retrospective study, the data of confounding factors, such as systemic lipid disorders, are not sufficiently collected, and the confounding factors cannot be analysed and discussed. In future studies, we need to collect various indicators of the subjects as much as possible and analyse and discuss the confounding factors in detail, so as to make the results of our study more credible.

In conclusion, ApoA1 and ApoE may be modifiable risk factors for PVR formation following primary RRD surgery. Consequently, our results underscore the importance of lipidaemic assessment prior to RD repair. Furthermore, it is imperative to implement preventative measures, such as disseminating health education regarding the impact of lipidaemic factors and smoking on ocular health, due to lack of awareness among the general public.

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