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ORIGINAL RESEARCH

Systemic Risk Factors for Vitreous Hemorrhage Secondary to Polypoidal Choroidal Vasculopathy

Baoyi Liu · Kunbei Lai · Yuan Ma · Kai Gao · Chinling Tsai · Jizhu Li · Xiaoyue Wei · Ziye Chen · Zitong Chen · Yaping Liu · Rebiya Tuxun · Tao Li

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ABSTRACT

Introduction: It remains unclear whether systemic factors are associated with an increased risk of vitreous hemorrhage (VH) secondary to polypoidal choroidal vasculopathy (PCV), and there is no method to predict the possibility of VH occurrence in patients with PCV. This study aimed to investigate and visualize systemic risk factors for VH in patients with PCV.

Methods: Data on the sex, age, history of systematic diseases, best-corrected visual acuity, intraocular pressure, and laboratory data of patients with PCV were collected from the medical record system. Univariate and multivariate binary logistic regression analyses were applied to investigate independent risk factors for VH in patients with PCV. Receiver operating characteristic analysis and nomograms were used to visualize the independent risk factors.

Results: The patient population comprised 115 patients with VH secondary to PCV and 181 patients with PCV without VH. Binary logistic regression analyses showed that higher white blood cell count [WBC; odds ratios (OR) 1.247], higher aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT; OR 2.339), and longer activated partial thromboplastin time (APTT; OR 1.196) were independent risk factors of VH in patients with PCV. Integrated application of APTT, AST/ALT, and WBC as markers showed the best performance for distinguishing patients with VH, with an area under the curve of 0.723. The nomogram was created for doctors to calculate the possibility of VH in a patient with PCV.

Conclusions: Higher WBC, higher AST/ALT, and longer APTT are independent serum risk factors of VH secondary to PCV, which may shed light on VH prevention in patients with PCV.

Keywords: Vitreous hemorrhage; Polypoidal choroidal vasculopathy; Risk factors; Nomogram

Baoyi Liu, Kunbei Lai and Yuan Ma have contributed equally to this work and are to be considered co-first authors.

B. Liu · K. Lai · Y. Ma · K. Gao · C. Tsai · J. Li · X. Wei · Z. Chen · Z. Chen · Y. Liu · R. Tuxun · T. Li (✉)
State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangzhou 510060, China
e-mail: litao2@mail.sysu.edu.cn

B. Liu · K. Lai · Y. Ma · K. Gao · C. Tsai · J. Li · X. Wei · Z. Chen · Z. Chen · Y. Liu · R. Tuxun · T. Li
Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou 510060, China

Key Summary Points

Why carry out this study?

Vitreous hemorrhage (VH) is one of the serious complications secondary to polypoidal choroidal vasculopathy (PCV), and can result in irreversible central visual acuity loss.

Although ocular risk factors have been identified, there is a lack of large sample data on systemic risk factors and there is no method to predict the possibility of VH occurrence.

We aimed to evaluate and visualize systemic risk factors for VH in patients with PCV and to provide ophthalmologists with the tools to make a timely intervention and educate patients with VH on the medical aspects.

What was learned from this study?

Higher white blood cell count, higher aspartate aminotransferase/alanine aminotransferase ratio, and longer activated partial thromboplastin time are independent serum risk factors for VH in patients with PCV.

A systemic nomogram was innovatively developed to help ophthalmologists prioritize care and attention to high-risk patients with PCV suffering from VH.

INTRODUCTION

Polypoidal choroid vasculopathy (PCV) is characterized by orange polypoid subretinal lesions with hemorrhagic or serous detachment of the retinal pigment epithelium and neuroepithelium [1]. The gold standard of diagnosing PCV is indocyanine green angiography (ICGA) showing an abnormal branching vascular network and terminal polypoid or aneurysmal dilatation [2, 3]. The incidence of PCV is higher in Asian than non-Asian populations. Among patients diagnosed with wet age-related macular degeneration (wAMD), the percentage of PCV diagnosed based on ICGA results is 4–13.9% in white patients and 22.3–61.6% in Asian patients [4].

Vitreous hemorrhage (VH) is one of the more serious complications secondary to PCV. The prognosis is poor since after VH, the eye with PCV gradually develops choroidal retinal atrophy and fibrous scar development, resulting in irreversible central visual acuity loss [5–7]. Previous research reported that 4.5–19.9% of patients with PCV developed VH [8, 9], necessitating pars plana vitrectomy (PPV) to improve visual acuity and prevent further complications, such as retinal detachment [5, 8, 10]. However, the final prognosis of visual acuity after PPV is still poor, despite the possibility of improvement in some cases. Consequently, early prevention of VH in patients with PCV is crucial.

The risk factors for VH in patients with PCV have been investigated on a preliminary level. A previous study revealed that one of the systemic risk factors for VH in PCV patients was older age of onset, but not systemic disease or medication history [11]. Some studies have demonstrated ocular risk factors included retinal pigment epithelium detachment, prior photodynamic therapy (PDT) and larger subretinal hemorrhage (SRH) area [9, 12]. However, there are as yet insufficient large sample data to investigate systemic risk factors for VH in individuals with PCV. In addition, there is no method to predict the possibility of VH occurrence in these patients.

This study therefore was a retrospective cross-sectional analysis of systemic risk factors for VH in patients with PCV, and developed a nomogram to assess the risk of VH in this patient population. The overall aim of this study was to provide tools that help ophthalmologists to intervene prior to the onset of VH in patients with PCV and to be able to better medically educate their patients on treatment adherence, so as to preserve patients' vision and maximize treatment benefit.

METHODS

This is a retrospective cross-sectional study conducted at Zhongshan Ophthalmic Center (ZOC) between November 2021 and March 2023. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committee of ZOC (reference number: 2023KYPJ021). Informed consent was obtained from all individual participants included in the study.

Assessment of PCV

Patients with PCV treated at ZOC from 2013 to 2021 were retrospectively included in the medical record system. Patients were eligible for inclusion in the study if they had been diagnosed with PCV based on the detection of hyperfluorescent dilated polypoidal lesion on ICGA. Due to the presence of VH, media opacity compromised the image quality of the fundus or angiography in most eyes at presentation. The VH was attributed to PCV based on the demonstration of polypoidal lesions on ICGA in the past or after PPV [3, 13, 14]. The exclusion criteria were: (1) any other concomitant ocular diseases that could confound the results pertaining to VH, such as wAMD, diabetic retinopathy, retinal artery or vein occlusion, Terson syndrome, macroaneurysms, uveitis, angioid streaks and severe hypertension, among others; (2) presence of ocular trauma or history of surgery, absence of blood test data, or the presence of systemic disorders other than hypertension, diabetes mellitus (DM) and coronary artery disease (CAD). The patients were divided into two groups. One group, designated the VH group, comprised patients with PCV diagnosed with VH via slit-lamp examination or fundus photography following full mydriasis, ocular B-scan ultrasound, or evaluation during PPV. The severity of VH was graded by ophthalmoscopy as: (1) grade 1, significant visibility of the fundus details; (2) grade 2, 50% of the retina visible; (3) grade 3, only peripheral retinal details visible; (4) grade 4, no fundal view possible. The second group of patients, designated the non-VH (NVH) group, comprised the remaining PCV patients with no diagnosis of VH. If a patient had bilateral PCV with VH in one eye, only the eye with VH was considered and the other eye with PCV was not included in the analysis. If a patient had bilateral PCV without VH, the PCV eye with the worse best-corrected visual acuity (BCVA) was included in the analysis, while the other PCV eye was excluded.

Data Collection

Data on sex, age, history of systematic diseases, medication use, smoking, alcohol consumption, BCVA (logMAR), intraocular pressure, and blood tests were extracted from each patient's medical record. The blood test data included: white blood cell count (WBC), red blood cell count (RBC), hemoglobin, platelet count, potassium (K^+), sodium (Na^+), fasting blood glucose (FBG), total protein, albumin, urea, creatinine), alanine aminotransferase (ALT), aspartate aminotransferase (AST), calculated AST/ALT ratio, prothrombin time (PT), international normalized ratio, activated partial thromboplastin time (aAPTT), fibrinogen and thrombin time, cholesterol, and triglyceride.

Statistical Analysis

Data analyses were conducted in SPSS software version 25.0 (SPSS IBM Corp., New York, NY, USA) and in R 4.2.1 with R packages rms, survival, lattice, formula, ggplot2, and hmisc. The normality of the data was tested by using the Shapiro–Wilk test and inspecting the histograms. Continuous data were summarized as the mean ± SD (standard deviation), while categorical data were presented as in specific quantity of each category. Independent *t*-tests and Mann–Whitney tests were used to compare normally distributed and non-normally distributed data, respectively. Chi-square (χ^2) analysis was used to compare categorical data. In all statistical analyses, significance was considered at the $p < 0.05$ level.

Nomogram Construction

To construct nomograms for the prediction of the risk of VH in patients with PCV, we conducted a several-step analysis of the relationship between the presence of VH and the risk factors. First, we carried out univariate binary logistic regression analyses in which we took the existence of VH as the dependent variable and all risk factors (see Table 1) as independent variables. Secondly, the variables, which were found to be statistically significant in the univariate analysis but not to mutually interfere were entered in the multivariate binary logistic regression analysis model. Outcomes of univariate and multivariate binary logistic regression analyses were expressed as odds ratios (ORs), 95% confidence intervals (95% CI), and p values. Thirdly, receiver operating characteristic (ROC) analysis was carried out to determine the performance of risk factors to distinguish patients with VH. The area under the ROC curve (AUC) was calculated. The optimal cutoff value was determined by the highest Youden index [(sensitivity + specificity) − 1], and the corresponding sensitivity and specificity values were recorded. Finally, nomograms for VH risk factors were developed using R packages, and the risk factors which were statistically significant in previous multivariate logistic regressions were selected as predictors. In the nomogram analyses, we treated the absence and presence of VH in patients with PCV as continuous variables ranging from 0 to 1, but not as categorical variables. The nomogram was constructed and then, as the last step, the score was plotted for each risk factor.

RESULTS

Demographic and Clinical Data Analyses

A total of 296 patients with PCV were enrolled in this study, including 181 patients in the NVH group and 115 patients in the VH group. The severity of VH was grade 3 in four VH eyes and grade 4 in the remaining 111 VH eyes. The demographic and clinical data of the two groups are shown in Table 1. There were no statistically significant differences between the two groups in terms of sex, age, history of systematic diseases, medication use, alcohol consumption, or eye laterality. In the VH group, the proportion of patients who smoked was higher ($p = 0.022$), and the BCVA was significantly worse ($p < 0.001$). For the routine blood test data, WBC was higher in the VH group. For the biochemical examination, FBG was lower in the VH group. In terms of liver and kidney function, AST and AST/ALT were higher in the VH group, suggesting a poor liver function in the VH group. For coagulation function, PT and APTT were prolonged and TT was shorter in the VH group. There was no significant difference in serum lipids between the two groups.

Logistic Regression Analyses

For those factors which different between the two groups, we used univariate binary logistic regression analysis to explore whether they were risk or protective factors for VH in patients with PCV. We considered that worse BCVA is the result of VH, but not a risk factor, and excluded BCVA in the logistic regression analysis. The univariate regression analyses (Table 2) showed higher WBC (OR 1.235), higher AST (OR 1.042), higher AST/ALT (OR 2.312), longer PT (OR 1.647), and longer APTT (OR 1.192) as the risk factors for VH in patients with PCV. These analyses also showed that lower RBC (OR 0.690) and shorter TT (OR 0.720) were protective factors for VH in patients with PCV.

After identifying the risk and protective factors for VH, we conducted the multivariate binary logistic regression analysis to determine whether each factor is an independent risk or independent protective factor for VH in these patients. To prevent the synergy between parameters from influencing the results, we selected a representative variable from each category (AST/ALT for liver function, APTT for coagulation function) for inclusion in the multivariate binary logistic regression analysis, according to the clinical significance and stepwise regression analyses. The multivariate regression analyses showed that higher WBC (OR 1.247), higher AST/ALT (OR 2.339), and

Table 1 Demographic and clinical data of the two groups (n = 296)

Patient characteristics	NVH group (n = 181)	VH group (n = 115)	p-value
Demographic characteristics			
Sex, n (female:male)	66:115	36:79	0.363
Age, years	63.86 ± 11.17	61.97 ± 10.44	0.145
Hypertension	69	50	0.395
DM, n	32	29	0.141
CAD, n	15	14	0.317
Anticoagulant medication, n	0	0	N/A
Antiplatelet medication, n	17	15	0.342
Smoking, n	49	46	0.022*
Alcohol consumption, n	41	16	0.070
Ocular characteristics			
Eye, n (OD: OS)	90:91	46:69	0.102
BCVA, LogMAR	0.98 ± 0.70	2.36 ± 0.56	< 0.001***
IOP, mmHg	13.13 ± 3.88	12.21 ± 4.81	0.070
Routine blood test			
WBC, 10^9/L	6.57 ± 1.42	7.14 ± 1.90	0.007**
RBC, 10^12/L	6.39 ± 12.45	4.84 ± 0.63	0.096
HGB, g/L	140.94 ± 14.71	142.63 ± 15.10	0.342
PLT, 10^9/L	241.41 ± 71.30	244.48 ± 66.30	0.711
Biochemistry			
K^+, mmol/L	4.29 ± 0.28	4.24 ± 0.39	0.166
Na^+, mmol/L	140.39 ± 2.33	139.99 ± 2.52	0.164
FBG, mmol/L	5.75 ± 1.30	5.45 ± 1.31	0.049*
Liver and kidney function			
TP, g/L	72.38 ± 3.70	73.24 ± 5.63	0.149
ALB, g/L	43.52 ± 2.48	43.11 ± 3.09	0.229
UREA, mmol/L	5.58 ± 1.56	5.45 ± 2.51	0.585
CREA, μmoI/L	76.11 ± 25.14	76.63 ± 41.10	0.893
ALT, U/L	25.82 ± 12.92	26.37 ± 16.23	0.747
AST, U/L	22.54 ± 7.06	25.08 ± 9.22	0.008**
AST/ALT	0.98 ± 0.33	1.14 ± 0.60	0.007**
Coagulation function			
PT, s	10.91 ± 1.38	11.27 ± 0.76	0.012*

Table 1 continued

Patient characteristics	NVH group (n = 181)	VH group (n = 115)	p-value
APTT, s	28.64 ± 4.64	31.31 ± 3.68	< 0.001***
TT, s	15.95 ± 1.90	14.71 ± 2.01	< 0.001***
FIB, g/L	3.00 ± 1.36	2.94 ± 0.65	0.673
INR	1.38 ± 3.26	1.01 ± 0.09	0.126
Serum lipids			
CHOL, mmol/L	4.99 ± 0.75	5.06 ± 1.02	0.522
TG, mmol/L	1.58 ± 0.91	1.78 ± 1.13	0.114

Values in table for the NVH and VH groups are given as the mean ± standard deviation (SD) or as a specific quantity (n patients), as appropriate

SD Standard deviation, *NVH* non-vitreous hemorrhage, *VH* vitreous hemorrhage, *DM* diabetes mellitus, *CAD* coronary artery disease, *BCVA* the best-corrected visual acuity, *logMAR* the logarithm of the minimum angle of resolution, *OD* oculus dextrus, *OS* oculus sinister, *IOP* intraocular pressure, *WBC* white blood cell count, *RBC* red blood cell count, *HGB* hemoglobin, *PLT* platelet count, K^+ potassium, Na^+sodium, *FBG* fasting blood glucose, *TP* total protein, *ALB* albumin, *UREA* urea, *CREA* creatinine, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AST/ALT* calculated aspartate aminotransferase/alanine aminotransferase ratio, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *TT* thrombin time, *FIB* fibrinogen, *INR* international normalized ratio, *CHOL* cholesterol, *TG* triglyceride

Significant difference at $^*p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$, respectively. Table shows a significantly worse BCVA, higher WBC, lower FBG, higher AST and AST/ALT, longer PT and APTT, and shorter TT in the VH group compared with the NVH group. There were no statistically significant differences between the two groups in terms of sex, age, eye laterality, or serum lipids

longer APTT (OR 1.196) were independent risk factors for VH in patients with PCV (Table 2).

ROC Analysis

An ROC analysis was performed for APTT, AST/ALT and WBC separately and for these factors integrated (Fig. 1). The ROC analysis of the integration of APTT, AST/ALT, and WBC showed the best performance for distinguishing the two groups of patients (VH vs. NVH), with an AUC of 0.723, sensitivity of 0.609 and specificity of 0.773. The AUC of APTT, AST/ALT, and WBC was 0.695, 0.580, and 0.567, respectively.

Nomogram Analysis

The risk factors which were statistically significant in the multivariate logistic regression (WBC, AST/ALT, and APTT) were selected as predictors of VH during the construction of the nomogram. Using the nomograms, doctors can optimize the feasibility of VH in a patient with PCV (Fig. 2a). The interpretation of these nomograms includes three main steps: (1) vertically connect the predictor's value (WBC, AST/ALT, and APTT) to the first row for a certain point; (2) calculate the total number of points; and (3) connect the total number of points to the final row to obtain a risk incidence value [15]. To assess the accuracy and validity of the nomogram, we constructed the calibration curves using bootstrap sampling, which is a re-sampling technique with retracting (shown in Fig. 2b). The result showed that the mean absolute error is 0.038 and that the curve when corrected for bias by bootstrapping is close to the entire sample curve, which suggests that the accuracy and validity of the nomogram are promising.

Table 2 Risk factors for vitreous hemorrhage in patients with polypoidal choroidal vasculopathy using binary logistic regression analysis (n = 296)

Patient characteristic	Univariate model, OR (95% CI)	p-value	Multivariate model, OR (95% CI)	p-value
Demographic characteristics				
Sex	1.259 (0.766–2.070)	0.363	N/A	N/A
Age, years	0.984 (0.963–1.006)	0.146	N/A	N/A
Hypertension	0.674 (0.420–1.082)	0.102	N/A	N/A
DM	1.570 (0.889–2.772)	0.120	N/A	N/A
CAD	1.534 (0.711–3.310)	0.276	N/A	N/A
Anticoagulant medication	N/A	N/A	N/A	N/A
Antiplatelet medication	1.447 (0.692–3.025)	0.326	N/A	N/A
Smoking	1.796 (1.093–2.951)	0.021*	1.176 (0.627–2.207)	0.613
Alcohol consumption	0.552 (0.293–1.039)	0.065	N/A	N/A
Ocular characteristics				
Eye laterality	0.674 (0.420–1.082)	0.102	N/A	N/A
BCVA, LogMAR	13.861 (8.8.057–23.847)	< 0.001***	N/A	N/A
IOP, mmHg	0.941 (0.879–1.006)	0.076	N/A	N/A
Routine blood test				
WBC, 10^9/L	1.235 (1.067–1.429)	0.005**	1.240 (1.028–1.496)	0. 024*
RBC, 10^12/L	0.690 (0.510–0.935)	0.017*	0.723 (0.515–1.017)	0.062
HBG, g/L	1.008 (0.992–1.024)	0.342	N/A	N/A
PLT, 10^9/L	1.001 (0.997–1.004)	0.710	N/A	N/A
Biochemistry				
K + , mmol/L	0.571 (0.273–1.196)	0.138	N/A	N/A
Na + , mmol/L	0.932 (0.844–1.029)	0.165	N/A	N/A
FBG, mmol/L	0.801 (0.638–1.007)	0.057	N/A	N/A
Liver and kidney function				
TP, g/L	1.043 (0.990–1.098)	0.116	N/A	N/A
ALB, g/L	0.946 (0.867–1.031)	0.207	N/A	N/A
UREA, mmol/L	0.965 (0.850–1.096)	0.587	N/A	N/A
CREA, μmoI/L	1.000 (0.993–1.008)	0.892	N/A	N/A
ALT, U/L	1.003 (0.987–1.019)	0.746	N/A	N/A
AST, U/L	1.042 (1.009–1.076)	0.013*	N/A	N/A

Table 2 continued

Patient characteristic	Univariate model, OR (95% CI)	*p*-value	Multivariate model, OR (95% CI)	*p*-value
AST/ALT	2.312 (1.295–4.129)	0.005**	2.083 (1.074–4.041)	0.030*
Coagulation function				
PT, s	1.647 (1.129–2.402)	0.010*	N/A	N/A
APTT, s	1.192 (1.111–1.279)	< 0.001***	1.166 (1.101–1.277)	< 0.001***
TT, s	0.720 (0.632–0.821)	< 0.001***	N/A	N/A
FIB, g/L	0.953 (0.763–1.191)	0.674	N/A	N/A
INR	0.338 (0.095–1.208)	0.095	N/A	N/A
Serum lipids				
CHOL, mmol/L	1.099 (0.839–1.441)	0.493	N/A	N/A
TG, mmol/L	1.216 (0.958–1.544)	0.109	N/A	N/A

Significant difference at $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$, respectively. The univariate regression analyses showed higher WBC (OR 1.235), higher AST (OR 1.042), higher AST/ALT (OR 2.312), longer PT (OR 1.647), and longer APTT (OR: 1.192) as the risk factors for VH in patients with PCV. The analyses also showed that lower RBC (OR 0.690) and shorter TT (OR 0.720) were the protective factors for VH in patients with PCV. The multivariate regression analyses showed that higher WBC (OR 1.247), higher AST/ALT (OR 2.339) and longer APTT (OR: 1.196) were the independent risk factors for VH in patients with PCV

OR Odds ratios, *95% CI* 95% confidence interval, *N/A* not available

DISCUSSION

To investigate and visualize the systemic risk factors of VH secondary to PCV, we performed a retrospective study using data collected from the medical records of 296 patients with PCV. Binary logistic regression analyses revealed that increased WBC, AST/ALT, and APTT were independent risk factors for VH in this patient population. In addition, we developed a nomogram for use by ophthalmologists to estimate the viability of VH in a patient with PCV. This nomogram will assist ophthalmologists in intervening before VH develops in patients with PCV and in educating patients to improve treatment adherence.

Two factors could account for the occurrence of VH secondary to PCV. First, animal experiments have demonstrated that VH in PCV occurs because the RBC fragments of the choroid layer break through the Bruch membrane and pass through the retinal layer to enter the vitreous cavity [16]. Second, the macular fovea and peripheral retina are the two retinal regions with the lowest histological strength [17]. Therefore, we hypothesized that the accumulated blood may enter the vitreous through the macular retina or the thin retina adjacent to the serrated edge. Increased intraocular pressure could cause the ruptured retina to reseal after bleeding. As a result of these processes, vitreous opacity could occur in the VH group, leading to worsening vision impairment.

For the three parameters identified as independent risk factors for VH, different pathways may lead to VH in patients with PCV. With respect to the increased WBC count, we believe that PCV patients with VH produce more WBC, including specific mononuclear macrophages and non-specific neutrophils, eventually forming blood flow stasis, which in turn increases vascular permeability and promotes the development of VH by interacting with the adhesion molecules of vascular endothelial cells [18, 19].

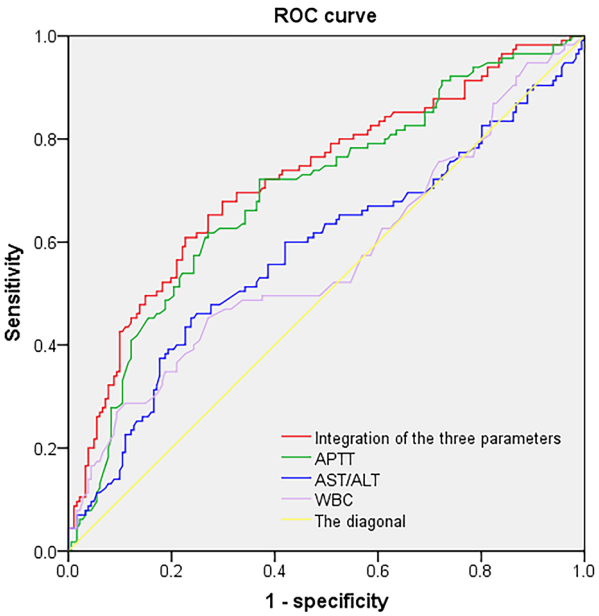

Fig. 1 Receiver operating characteristic (*ROC*) curve of risk factors for distinguishing patients with vitreous hemorrhage (*VH*) from those without VH (*NVH*). The area under the ROC curve (AUC) of activated partial thromboplastin time (*APTT*), calculated aspartate aminotransferase/alanine aminotransferase ratio (*AST/ALT*), and white blood cell (*WBC*) count is 0.695, 0.580 and 0.567, respectively. The AUC of the integration of these three parameters is 0.723, with a sensitivity of 0.609 and specificity of 0.773.

The rise in AST/ALT levels in PCV patients with VH may be attributable to a deterioration in liver function, which can lead to a decrease in the generation of coagulation factors and then to coagulation dysfunction [20]. Once choroid or subretinal hemorrhage starts, the amount of bleeding will increase, leading to greater hemorrhage, which is more susceptible to VH. PT and APTT prolongation, and TT shortening suggest that the coagulation function in the VH group may be impaired. Considering that PCV patients lack visible traumatic wounds and have not been exposed to exogenous agents that promote extrinsic coagulation pathways, it is extremely probable that modifications to the fibrinolytic system related to endogenous coagulation pathways disorders (as indicated by an extended APTT) will develop [21]. To summarize, it is understandable that higher WBC, higher AST/ALT, and longer APTT are the independent serum risk factors for VH secondary to PCV.

Previous studies have shown that smoking, hypertension, diabetes, cardiovascular disease, and anticoagulant medications are not correlated with VH in patients with PCV, as also shown in the present study [9, 11, 12]. Based on the results of previous studies, we further assessed blood indicators that are objective and dependable by reducing patient retrospective error and analysis bias of their medical history. The relevance of our study on systemic risk factors for VH in patients with PCV lies in the suggestion that patients with PCV with high WBC and impaired coagulation function should pay more attention to the probability of VH. With the help of our nomogram, high-risk patients with PCV should actively cooperate with ophthalmologists in adhering to a treatment plan before the occurrence of VH, such as prompt anti-vascular endothelial growth factor (VEGF) therapy or combined therapy, with the aim to effectively limit the progression of PCV [22–25].

The strength of our study is that three specific systemic parameters, namely, higher WBC, higher AST/ALT, and longer APTT, were identified as independent factors that increase the risk of VH in patients with PCV, and the pictorial nomogram has been used for the first time to predict VH in PCV patients. However, there are several limitations in our study. First, our study failed to elucidate the causative connections between the factors and VH, which is a common deficiency of cross-sectional studies. Therefore, a prospective cohort study will be conducted in the future to validate the results of this baseline study. Secondly, we did not incorporate ocular risk variables, such as OCT values and VH grading, into our analysis. Due to the massive VH that can occur in patients with PCV, which can readily reach VH grade 4, it is difficult to obtain information on the area of subretinal hemorrhage from fundus photography and on the retinal pigment epithelium and choroid from OCT examination. Thirdly, all subjects were included in the ZOC in China, which may have resulted in a selection bias. To uncover more precise results, it is necessary to

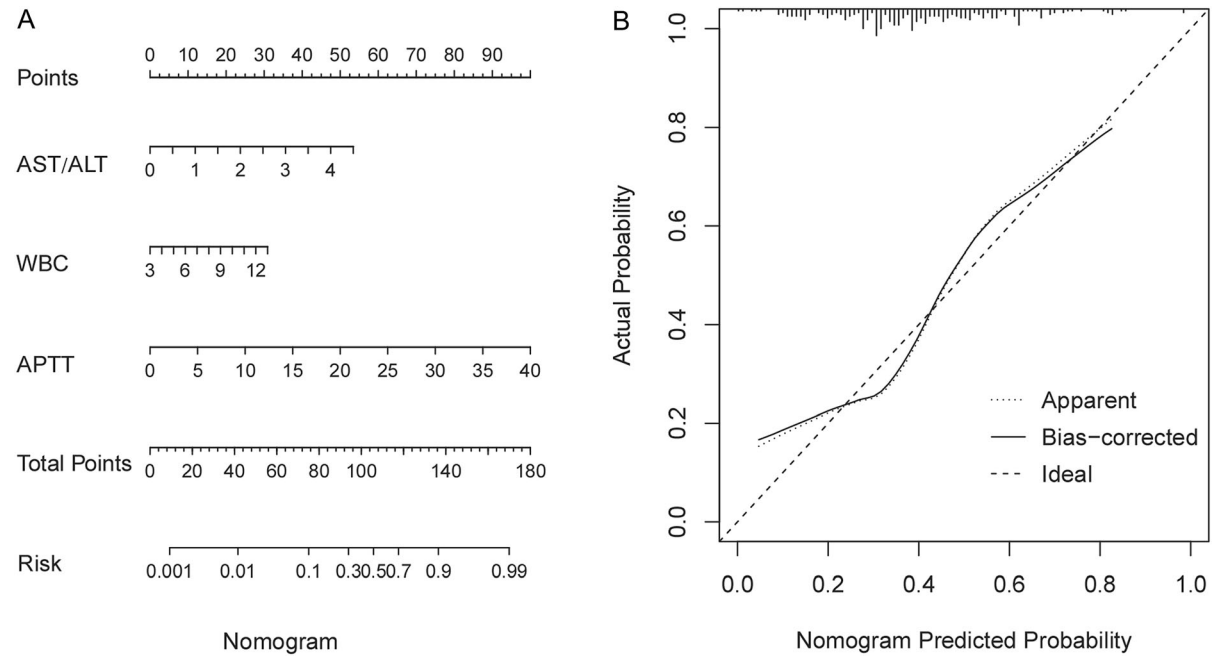

Fig. 2 Nomogram for the risk of VH in patients with PCV. **a** The nomogram for calculating the possibility of VH in a patients with PCV. The interpretation of this nomogram includes 3 main steps: 1) vertically connect the predictor's value (WBC, AST/ALT, and APTT) to the first row for a certain point; (2) calculate the total number of points; and (3) link the total number of points to the final row to obtain a numerical risk incidence value. **b** The calibration curves for the nomogram. The *x*-axis represents the nomogram-predicted probability and the *y*-axis represents the actual probability of VH in patients with PCV. Perfect prediction corresponds to the 45° dashed line. The dotted line represents the entire sample (n = 296), and the solid line is corrected for bias by bootstrapping (β = 1000 repetitions), indicating observer nomogram performance. The mean absolute error was 0.038

do further research on a wider range of populations in other locations.

CONCLUSION

Higher WBC, higher AST/ALT, and prolonged APTT were found to be independent, systemic risk factors for VH secondary to PCV. The innovative nomogram can provide direct guidance to ophthalmologists and enable them to intervene timely and also to provide better medical guidance to patients with PCV, possibly leading to the avoidance of VH incidence and thus to preserving patients' vision and optimization of treatment.

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Conflict of Interest. All named authors confirm that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article to declare.

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