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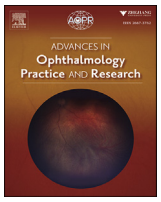

Full Length Article

Construction and validation of risk prediction models for different subtypes of retinal vein occlusion

Chunlan Liang [a], Lian Liu [a], Wenjuan Yu [a], Qi Shi [a], Jiang Zheng [a], Jun Lyu [b,*], Jingxiang Zhong [a,c,**]

[a] Department of Ophthalmology, The First Affiliated Hospital of Jinan University, Guangzhou, China
[b] Department of Clinical Research, The First Affiliated Hospital of Jinan University, Guangzhou, China
[c] Department of Ophthalmology, The Sixth Affiliated Hospital of Jinan University, Dongguan, China

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ABSTRACT

Purpose: While prognostic models for retinal vein occlusion (RVO) exist, subtype-specific risk prediction tools for central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) remain limited. This study aimed to construct and validate distinct CRVO and BRVO risk stratification nomograms.

Methods: We retrospectively analyzed electronic medical records from a tertiary hospital in Guangzhou (January 2010–November 2024). Non-RVO controls were matched 1:4 (CRVO) and 1:2 (BRVO) by sex and year of admission. The final cohorts included 630 patients (126 CRVO cases and 504 controls) and 813 patients (271 BRVO cases and 542 controls). Predictors encompassed clinical histories and laboratory indices. Multivariate regression identified independent risk factors, and model performance was evaluated using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis (DCA).

Results: The CRVO-nom and BRVO-nom highlighted significant predictors, including the neutrophil-to-lymphocyte ratio (NLR). Additional risk factors for CRVO included high-density lipoprotein cholesterol (HDL-C), platelet distribution width (PDW), history of diabetes, cerebral infarction, and coronary artery disease (CAD). For BRVO, significant predictors included a history of hypertension, age, and body mass index (BMI). The AUC for CRVO-nom was 0.80 (95% CI: 0.73–0.87) in the training set and 0.77 (95% CI: 0.65–0.86) in the validation set, while BRVO-nom yielded an AUC of 0.95 (95 %CI: 0.91–0.97) in the training set and 0.95 (95% CI: 0.89–0.98) in the validation set.

Conclusions: CRVO and BRVO exhibit distinct risk profiles. The developed nomograms—CRVO-nom and BRVO-nom—provide subtype-specific risk stratification with robust discrimination and clinical applicability. An online Shiny calculator facilitates real-time risk estimation, enabling targeted prevention for high-risk populations.

1. Introduction

Retinal vein occlusion (RVO) is a major retinal vascular disease that leads to irreversible visual impairment, with an annual incidence of approximately 0.1%.[1] RVO manifests in two primary subtypes: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), which differ significantly in their pathological mechanisms and clinical manifestations.[2] CRVO involves the central retinal vein and is often associated with extensive retinal hemorrhages and macular edema, resulting in more severe visual outcomes. In contrast, BRVO affects a branch of the retinal vein and typically has a better visual prognosis due to its localized nature.[3] Systemic risk factors such as hypertension, diabetes mellitus, and hyperlipidemia are closely associated with the onset of RVO.[4,5] Despite advancements in treatment options, including anti-VEGF drugs and laser photocoagulation, significant challenges remain.[6–8] These include delayed diagnosis, high recurrence rates, and substantial interindividual variability in treatment efficacy. Therefore, early identification of high-risk populations and the development of individualized intervention strategies are critical for improving RVO outcomes.

In recent years, artificial intelligence (AI)-driven clinical predictive

* Corresponding author.
** Corresponding author. Department of Ophthalmology, The First Affiliated Hospital of Jinan University, 613 Huangpu Road, Guangzhou, 510630, Guangdong Province, China.
E-mail addresses: lyujun2020@jnu.edu.cn (J. Lyu), zjx85221206@126.com (J. Zhong).

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models have demonstrated significant value in the management of ocular diseases.[9] For instance, deep learning models based on optical coherence tomography (OCT) images have shown remarkable accuracy in predicting the progression of glaucoma.[10] Similarly, integrating clinical data, demographic characteristics, and laboratory indicators has significantly enhanced risk stratification accuracy in diabetic retinopathy (DR).[11] In the field of RVO, several studies have attempted to predict treatment responses to anti-VEGF therapy using clinical indicators (*e.g.*, baseline visual acuity and central macular thickness) and imaging features (*e.g.*, hyperreflective foci).[12–14] However, these models primarily focus on predicting treatment outcomes, such as visual recovery and recurrence risk,[15] rather than assessing the risk of RVO occurrence itself. This leaves a critical gap in the ability to identify individuals at high risk of developing RVO before the onset of symptoms, which is essential for preventive interventions.

Despite some progress in RVO risk prediction, existing models often lack subtype specificity, limiting their clinical utility. For example, Shao et al.[16] developed a nomogram that integrates indicators of HDL levels, neutrophil counts, and hypertension to predict RVO risk. While their model demonstrated reasonable predictive accuracy (C-index = 0.74), it failed to distinguish between independent risk factors for CRVO and BRVO, resulting in inadequate subtype-specific risk stratification. This limitation underscores the need for subtype-specific predictive tools that can provide more precise risk assessments and guide targeted preventive strategies.

This study aims to address this gap by developing predictive models specifically tailored to assess the risk of incidence of CRVO and BRVO subtypes. Key innovations of this research include the use of independent cohorts for subtype-specific modeling and the integration of multidimensional data, such as clinical histories and laboratory indicators, to enhance predictive accuracy. Additionally, we will create a real-time risk assessment tool through a Shiny web calculator, offering a practical solution for clinical decision-making. By addressing the existing limitations in subtype-specific risk prediction, this research seeks to provide user-friendly scoring tools that enable targeted prevention strategies for high-risk populations, ultimately improving outcomes for patients with RVO.

2. Methods

2.1. Source of data

This study retrospectively analyzed electronic medical records from a tertiary hospital in Guangzhou (January 2010 to November 2024). Non-RVO controls were prioritized for matching by sex (ensuring similar sex distribution) and year of admission (to control for temporal trends in clinical practice), with case-to-control ratios set at 1:4 for CRVO and 1:2 for BRVO to optimize statistical power.[17] The final cohorts comprised 126 CRVO cases (504 controls) and 271 BRVO cases (542 controls). The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (2024-IIT-011) and adhered to the principles of the Declaration of Helsinki, ensuring that all ethical considerations were upheld throughout the research process.

2.2. Participants

2.2.1. Inclusion criteria

RVO Patients: Diagnosed with CRVO (ICD-9362.35) or BRVO (ICD-9362.36) based on ICD-9-CM criteria.

Non-RVO Controls: No history of RVO and had undergone comprehensive ophthalmologic examinations.

2.2.2. Exclusion criteria

RVO Patients: (1) Presence of other ocular diseases (*e.g.*, DR, retinal detachment). (2) Incomplete clinical data.

Non-RVO Controls: Same exclusion criteria as RVO patients, excluding RVO diagnosis.

2.3. Predictors

The predictive model incorporated the following variables:

Clinical Data: Sex, age, history of hypertension, diabetes, hyperlipidemia, coronary artery disease (CAD), carotid atherosclerosis or stenosis, cerebral infarction, chronic kidney disease (CKD), glaucoma, and body mass index (BMI).

Laboratory Indicators: Red blood cell count (RBC), white blood cell count (WBC), hematocrit (HCT), mean corpuscular volume (MCV), hemoglobin (Hgb), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW-CV), monocyte count (MONO), lymphocyte count (LYM), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), neutrophil count (NEU), creatinine (CREA), blood urea nitrogen (UREA), uric acid (UA), glucose (GLU), triglyceride (TG), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Derived Ratios: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic immune-response index (SIRI), and monocyte-to-high-density lipoprotein cholesterol ratio (MHR). These were calculated as follows:

$$NLR = NEU / LYM$$

$$PLR = PLT / LYM$$

$$LMR = LYM / MONO$$

$$SII = PLT \times NLR$$

$$SIRI = MONO \times NLR$$

$$MHR = MONO / HDL\text{-}C$$

2.4. Main outcome measures

Logistic regression models were developed to predict the risk of RVO subtype occurrence. Model performance was evaluated using the area under the curve (AUC), calibration plots, and decision curve analysis (DCA).

2.5. Statistical analysis methods

The CRVO-nom and BRVO-nom models were developed and validated using R software (version 4.3.3) and Python (version 3.8). The dataset was randomly divided into training (70%) and validation (30%) sets using the "caret" package (version 6.0–94).

(1) Correlation Analysis: Pearson correlation coefficients between variables were calculated and visualized as a matrix heat map to assess multicollinearity. Variables with high correlation ($|r| > 0.8$) were carefully evaluated to avoid overfitting.[18]
(2) Model Development: Univariate and multivariate regression analyses were performed using the "stats" package (version 4.3.3) to identify predictors. Variable selection was conducted using four methods: Enter, Forward, Backward, and Stepwise (Both) regression. The performance of each variable selection method was evaluated by comparing the Akaike Information Criterion (AIC) of the resulting models.[19]

The model yielding the lowest AIC, which indicates an optimal balance between model fit and complexity, was prioritized for final model development.[19] In cases where multiple models had similar AIC values, the model with fewer variables was preferred to enhance interpretability

and usability.

(3) Model Validation: The AUC with bootstrap 95% confidence intervals (CI) was assessed using the "scikit-learn" package (version 1.3.2). Calibration diagrams were generated using the "rms" package (version 6.7–1), and model calibration was evaluated with the Hosmer-Lemeshow test ("ResourceSelection" package, version 0.3–6). DCA was performed using the "rmda" (version 1.6) and "PredictABEL" (version 1.2–4) packages to compare the predictive power of the models.
(4) Presentation and Interpretation: Nomograms for CRVO and BRVO were constructed using the "rms" package. Shapley Additive exPlanations (SHAP) values were calculated and visualized using the "shap" package (version 0.44.1) in Python to interpret feature contributions and enhance model interpretability.[20]
(5) Clinical Implementation: The models were integrated into a free, user-friendly Shiny web application, enabling clinicians to input features and obtain predicted CRVO/BRVO risk probabilities.

3. Results

3.1. Patient characteristics

The study included 630 patients (126 CRVO cases vs. 504 controls) and 813 patients (271 BRVO cases vs. 542 controls) for CRVO-nom and BRVO-nom development, respectively. Both cohorts were randomly split into training/validation sets at a 7:3 ratio (CRVO: 441/189; BRVO: 570/243). Baseline characteristics showed no significant differences between training and validation sets ($P > 0.05$ for almost all variables), confirming balanced cohort allocation. For further details, please refer to the Supplementary Tables 1 and 2

3.2. Correlation Analysis between variables

We calculated the Pearson correlation coefficients for each variable and utilized the "ggplot2" library to create a matrix heatmap. The heatmap visually represents the pairwise correlations, with blue indicating positive correlations and red indicating negative correlations. The intensity of the colors corresponds to the strength of the correlation, where values close to +1 (dark blue) and −1 (dark red) reflect strong positive and negative relationships, respectively. Variables with absolute correlation coefficients >0.8 were considered strongly correlated, including derived ratios, WBC and NEU, MCV and MCH, HCT and Hgb, with full details provided in Supplementary Figs. 1 and 2.

3.3. Establishment of the model

Both univariate and multivariate regression analyses were conducted to identify predictors for CRVO and BRVO. The results indicated that NLR, PDW, history of diabetes, cerebral infarction, and CAD were

Table 1
Univariate and multivariate regression analysis for the predictor of CRVO-nom in the training set.

Variable name	Univariate regression analysis			Multivariate regression analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.04	1.02–1.06	<0.001***	–	–	–
ALT	0.99	0.98–1.01	0.526	–	–	–
AST	0.98	0.94–1.01	0.15	–	–	–
BMI	1.06	0.99–1.14	0.113	–	–	–
CHOL	0.8	0.62–1.03	0.078	–	–	–
CREA	1	1–1.01	0.264	–	–	–
GLU	1.33	1.17–1.52	<0.001***	–	–	–
HCT	0.99	0.94–1.05	0.714	–	–	–
HDL-C	0.06	0.02–0.17	<0.001***	0.09	0.03–0.3	<0.001***
Hgb	1	0.98–1.01	0.569	–	–	–
History of CAD (Yes)	4.9	2.01–11.95	<0.001***	3.09	1.1–8.65	0.032*
History of carotid atherosclerosis or stenosis (Yes)	4.23	1.33–13.45	0.015*	–	–	–
History of cerebral infarction (Yes)	8.26	2.96–23.03	<0.001***	5.93	1.86–18.87	0.003**
History of CKD (Yes)	2.6	0.83–8.14	0.102	–	–	–
History of diabetes (Yes)	4.46	2.19–9.08	<0.001***	3.16	1.34–7.48	0.009**
History of glaucoma (Yes)	8.54	2.09–34.87	0.003**	–	–	–
History of hyperlipidemia (Yes)	4.94	1.74–14.02	0.003**	–	–	–
History of hypertension (Yes)	4.3	2.64–7.02	<0.001***	1.49	0.81–2.74	0.196
LDL-C	0.91	0.65–1.26	0.554	–	–	–
LMR	0.78	0.69–0.88	<0.001***	–	–	–
LYM	0.39	0.24–0.61	<0.001***	–	–	–
MCH	1.03	0.94–1.13	0.512	–	–	–
MCHC	0.99	0.97–1.01	0.45	–	–	–
MCV	1.02	0.98–1.06	0.244	–	–	–
MHR	21.73	4.96–95.23	<0.001***	–	–	–
MONO	3.38	0.78–14.7	0.105	–	–	–
MPV	1.43	1.11–1.86	0.007*	–	–	–
NEU	1.4	1.19–1.64	<0.001***	–	–	–
NLR	1.56	1.29–1.89	<0.001***	1.5	1.24–1.83	<0.001***
PDW	1.21	1.1–1.33	<0.001***	1.13	1.02–1.26	0.018*
PLR	1	1–1.01	0.292	–	–	–
PLT	0.99	0.99–1	<0.001***	1	0.99–1	0.076
RBC	0.71	0.47–1.09	0.122	–	–	–
RDW-CV	0.94	0.77–1.13	0.494	–	–	–
Sex (Male)	1.05	0.66–1.68	0.83	–	–	–
SII	1	1–1.01	0.029*	–	–	–
SIRI	1.78	1.34–2.39	<0.001***	–	–	–
TG	1.09	0.93–1.28	0.277	–	–	–
UA	1	1–1.01	0.6	–	–	–
UREA	1.08	0.98–1.19	0.1	–	–	–
WBC	1.17	1.02–1.35	0.028*	–	–	–

*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$.

identified as independent risk factors, while HDL-C was recognized as a protective factor in CRVO-nom (Table 1). For BRVO, a history of hypertension, age, NLR, and BMI emerged as independent risk factors (Table 2). Due to the correlation between NEU and NLR (Pearson correlation coefficient = 0.62), we included NLR in the final BRVO-nom model while excluding NEU.

3.4. Validation of the model

The CRVO-nom achieved a bootstrap AUC of 0.80 (95% CI: 0.73–0.87) in the training set and 0.77 (95% CI: 0.65–0.86) in the validation set (Fig. 1A). The BRVO-nom demonstrated higher discriminative ability, with AUCs of 0.95 (95% CI: 0.91–0.97) and 0.95 (95% CI: 0.89–0.98) in training and validation sets, respectively (Fig. 2A).

Calibration plots indicated alignment between the nomogram predictions and actual observations in both the training and validation cohorts ($P > 0.05$). The Hosmer-Lemeshow test confirmed no significant differences between predicted and observed probabilities for either model: CRVO-nom training set: $P = 0.169$, validation set: $P = 0.071$ (Fig. 1B); BRVO-nom training set: $P = 0.052$, validation set: $P = 0.428$ (Fig. 2B).

Furthermore, DCA revealed clinical utility across threshold probabilities. As illustrated in Fig. 1C, the CRVO-nom model demonstrated superior net benefits compared to both the "Treat All" and "None" strategies within threshold probability ranges of 0.1–0.9 in the training set and 0.1–0.65 in the validation set. Similarly, the BRVO-nom model (Fig. 2C) showed a higher net benefit at 0.1–0.9 (training set) and 0.1–0.7 (validation set) thresholds, with stable performance in plateau phases.

3.5. Visualization and interpretation of the model

The CRVO-nom incorporated six variables. For example, in a patient with CAD, diabetes, PDW = 11.70 fL, NLR = 2.34, HDL-C = 0.92 mmol/L, and no cerebral infarction history, the estimated risk of CRVO was 87.9% (Fig. 3A). SHAP analysis identified HDL-C, NLR, PDW, diabetes, and cerebral infarction as top predictors (Fig. 3B). Lower HDL-C, elevated NLR/PDW, and diabetes/cerebral infarction/CAD history increased CRVO risk.

The BRVO-nom included four variables. A 46-year-old patient with hypertension, BMI = 24.73 kg/m^2, and NLR = 1.7 showed an estimated BRVO risk of 86.1% (Fig. 4A). SHAP analysis prioritized hypertension, age, NLR, and BMI (Fig. 4B) with hypertension and higher age/NLR/BMI elevating BRVO risk.

4. Discussion

In this study, we developed two distinct nomograms—CRVO-nom (HDL-C, NLR, PDW, diabetes, cerebral infarction, CAD) and BRVO-nom (hypertension, age, NLR, BMI)—to address the unmet need for subtype-specific RVO risk stratification. These models integrate easily

Table 2
Univariate and multivariate regression analysis for the predictor of BRVO-nom in the training set.

Variable name	Univariate regression analysis			Multivariate regression analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.15	1.13–1.18	<0.001***	1.12	1.08–1.16	<0.001***
ALT	1	0.99–1.01	0.965	–	–	–
AST	0.99	0.98–1.01	0.514	–	–	–
BMI	1.2	1.13–1.26	<0.001***	1.11	1.01–1.22	0.031*
CHOL	0.65	0.55–0.78	<0.001***	–	–	–
CREA	1.02	1.01–1.03	<0.001***	–	–	–
GLU	1.73	1.46–2.04	<0.001***	–	–	–
HCT	0.94	0.9–0.98	0.009**	–	–	–
HDL-C	0.41	0.23–0.76	0.004**	–	–	–
Hgb	0.98	0.97–1	0.011*	–	–	–
History of CAD (Yes)	39078556.88	0-Inf	0.973	–	–	–
History of carotid atherosclerosis or stenosis (Yes)	13434896.67	0-Inf	0.972	–	–	–
History of cerebral infarction (Yes)	38345833.94	0-Inf	0.975	–	–	–
History of CKD (Yes)	36959839.94	0-Inf	0.98	–	–	–
History of diabetes (Yes)	44.38	10.51–187.42	<0.001***	–	–	–
History of glaucoma (Yes)	13199196.73	0-Inf	0.976	–	–	–
History of hyperlipidemia (Yes)	38107661.05	0-Inf	0.976	–	–	–
History of hypertension (Yes)	255.01	78.52–828.21	<0.001***	136.17	35.35–524.45	<0.001***
LDL-C	0.56	0.44–0.72	<0.001***	–	–	–
LMR	0.71	0.64–0.78	<0.001***	–	–	–
LYM	0.33	0.24–0.46	<0.001***	–	–	–
MCH	0.99	0.92–1.07	0.835	–	–	–
MCHC	0.99	0.97–1.01	0.191	–	–	–
MCV	1	0.98–1.03	0.759	–	–	–
MHR	32.75	9.49–113.04	<0.001***	–	–	–
MONO	7.22	2.28–22.86	0.001**	–	–	–
MPV	1.7	1.33–2.17	<0.001***	1.45	0.93–2.26	0.103
NEU	1.31	1.14–1.51	<0.001***	0.53	0.34–0.81	0.004**
NLR	2.37	1.89–2.99	<0.001***	4.18	2.44–7.15	<0.001***
PDW	1.35	1.23–1.49	<0.001***	–	–	–
PLR	1	1–1.01	0.014*	–	–	–
PLT	0.98	0.98–0.99	<0.001***	0.99	0.99–1	0.103
RBC	0.71	0.5–0.99	0.044*	–	–	–
RDW-CV	0.99	0.83–1.19	0.929	–	–	–
Sex (Male)	1	0.7–1.43	0.982	–	–	–
SII	1	1–1.01	<0.001***	–	–	–
SIRI	3.6	2.47–5.26	<0.001***	–	–	–
TG	1.32	1.11–1.57	0.002**	–	–	–
UA	1	1–1.01	0.648	–	–	–
UREA	1.46	1.29–1.66	<0.001***	–	–	–
WBC	1.04	0.94–1.16	0.431	–	–	–

*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$.

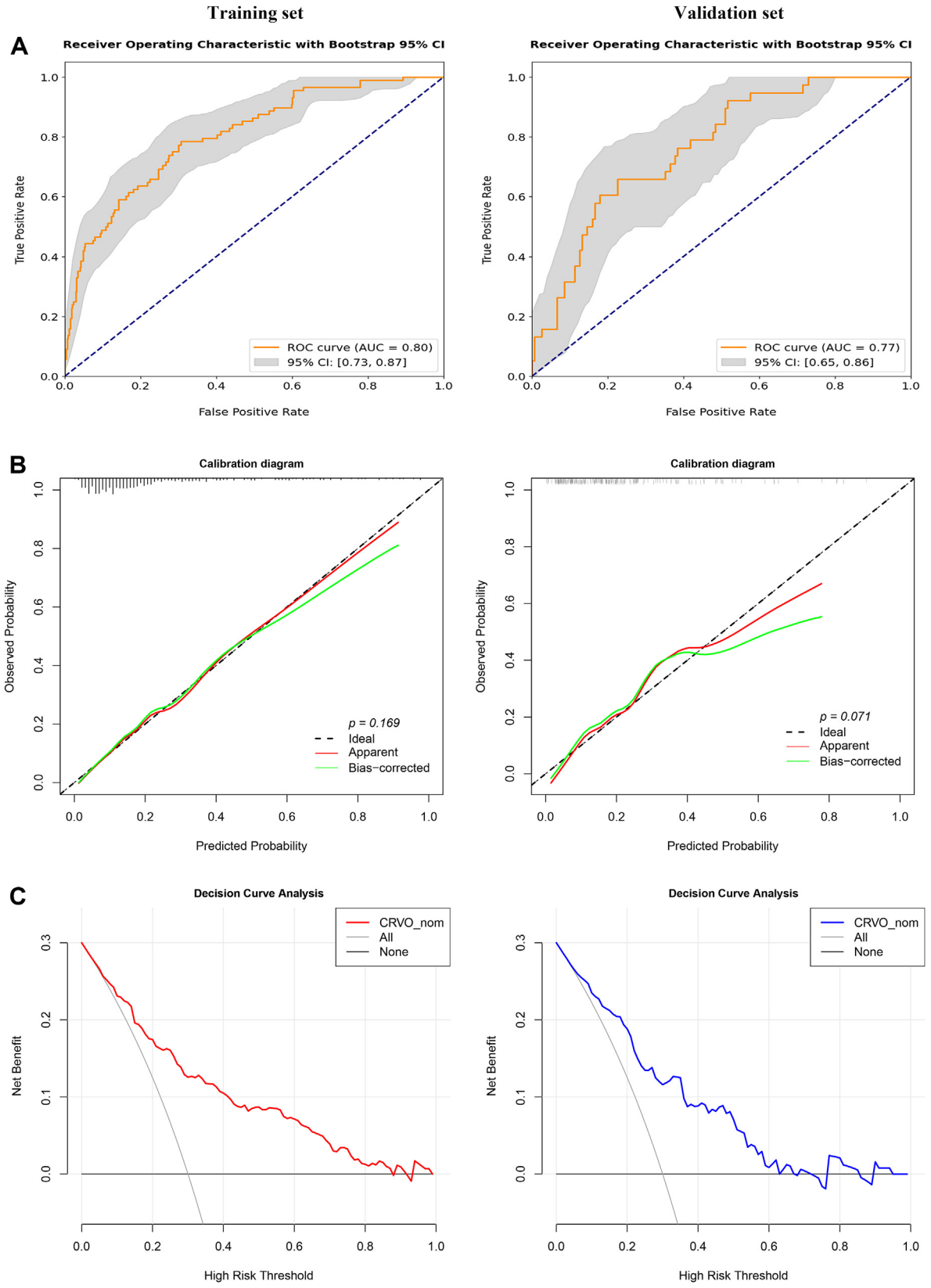

Fig. 1. Performance Evaluation of Central Retinal Vein Occlusion (CRVO)-nom Prediction Model
(A) Receiver Operating Characteristic (ROC) Curve; Solid curve: CRVO-nom; Gray shaded area: 95% CI (Bootstrap, 1000 replicates); Dashed diagonal: Random reference (AUC = 0.5).
(B) Calibration Plot; Dashed diagonal: Perfect prediction; Red curve: Original model; Green curve: Bootstrap-corrected; Histogram (background): Distribution of predicted probabilities.
(C) Decision Curve Analysis (DCA); Gray curve: Treat all; Black curve: Treat none; Color curves: CRVO-nom net benefit.

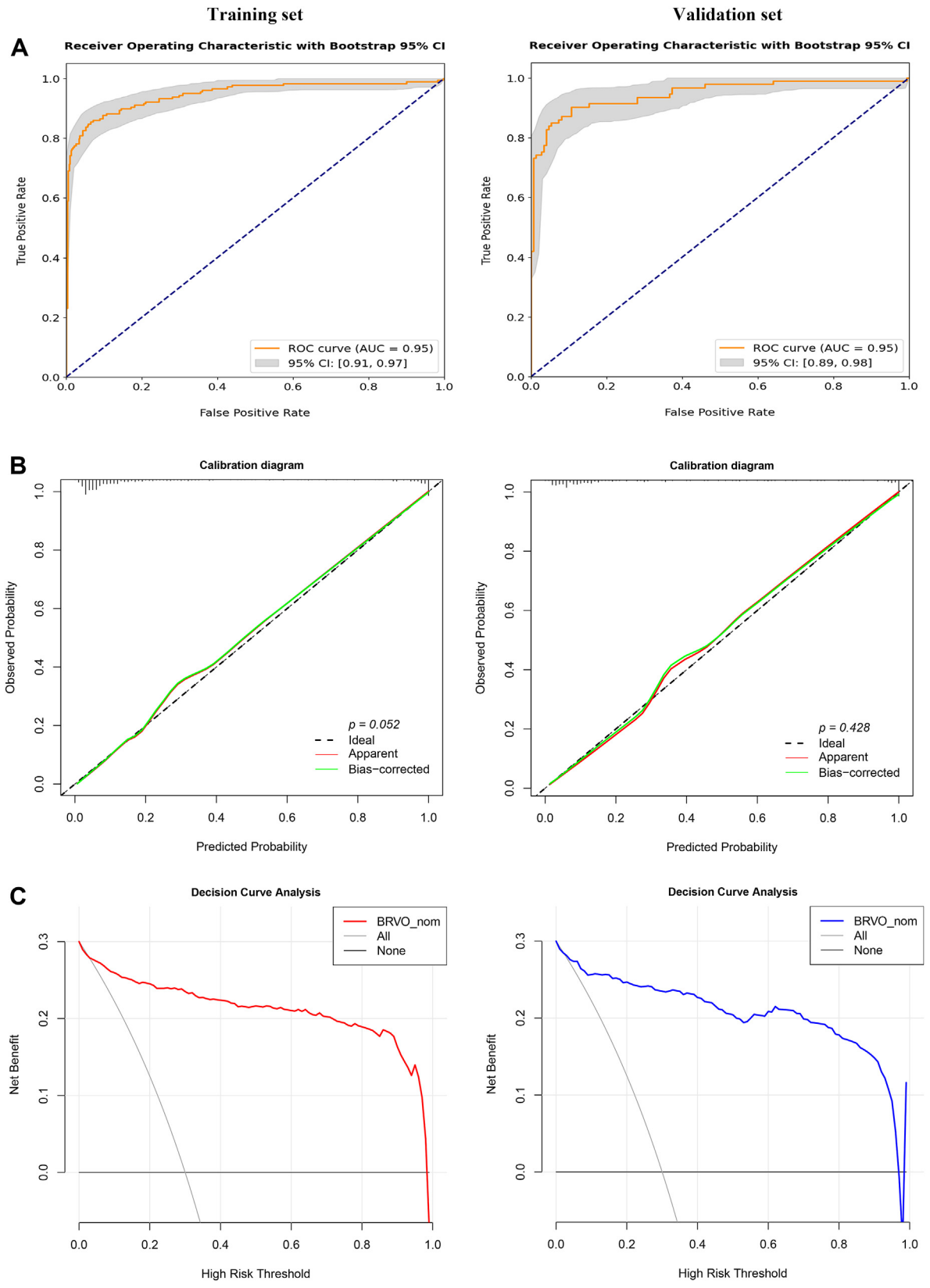

Fig. 2. Performance Evaluation of Branch Retinal Vein Occlusion (BRVO)-nom Prediction Model
(A) ROC Curve; Solid curve: BRVO-nom; Gray shaded area: 95% CI (Bootstrap, 1000 replicates); Dashed diagonal: Random reference (AUC = 0.5).
(B) Calibration Plot; Dashed diagonal: Perfect prediction; Red curve: Original model; Green curve: Bootstrap-corrected; Histogram (background): Distribution of predicted probabilities.
(C) DCA; Gray curve: Treat all; Black curve: Treat none; Color curves: BRVO-nom net benefit.

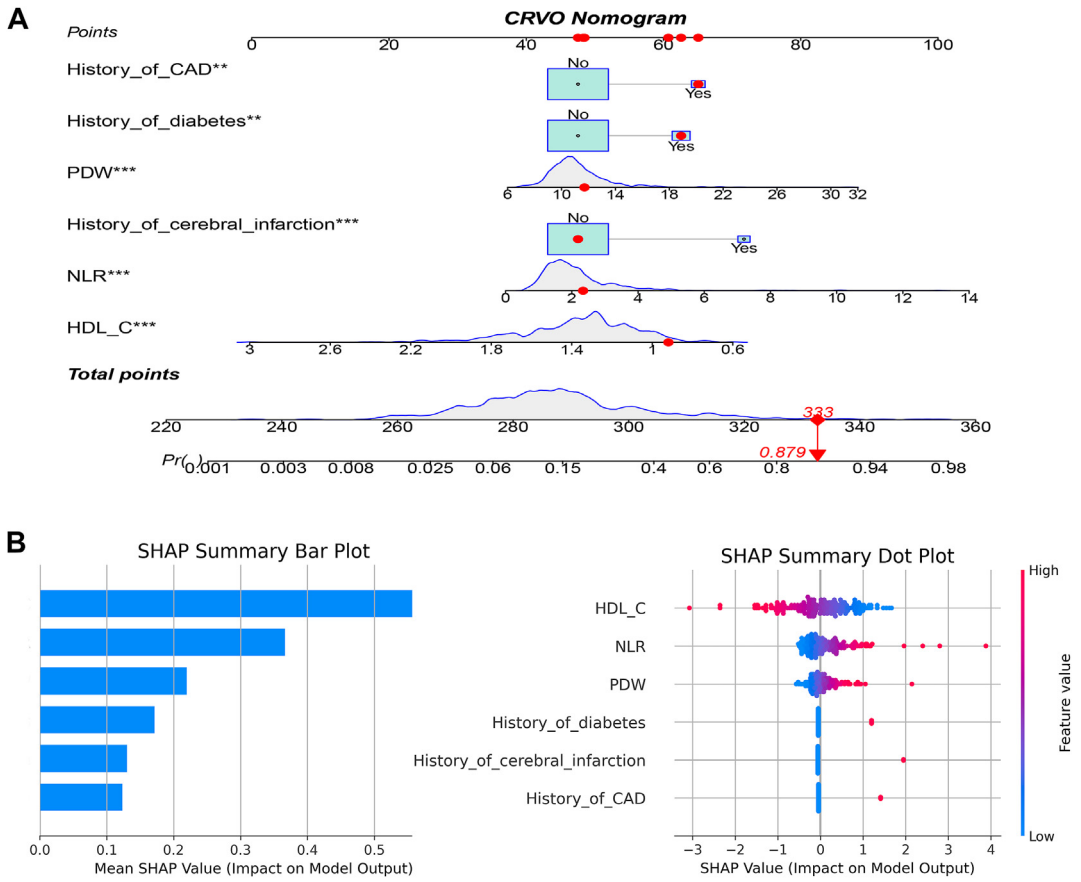

Fig. 3. CRVO-nom Presentation and Interpretation **(A) Dynamic nomogram example**: An individual with coronary artery disease (CAD), diabetes, PDW = 11.70 fL, Neutrophil to lymphocyte ratio (NLR) = 2.34, HDL-C = 0.92 mmol/L, and no cerebral infarction history has an 87.9% CRVO risk. **(B) Shapley Additive exPlanations (SHAP) based global interpretation**: The bar chart ranks features by average SHAP value; the dot plot shows rising CRVO risk with feature changes—red (higher values) and blue (lower values). Vertical stacking reflects value density.

obtainable clinical and hematologic variables, achieving robust discrimination (CRVO AUC: 0.77–0.80; BRVO AUC: 0.95). More importantly, the free-access online calculators were developed using the dynamic nomogram (https://chunlanliang.shinyapps.io/CRVO_Risk/) and (https://chunlanliang.shinyapps.io/BRVO_Risk/), enabling users to obtain CRVO/BRVO risk predictions quickly and conveniently. Below, we dissect the mechanistic roles of key predictors, contrast findings with existing literature, and highlight the clinical implications of our models.

4.1. NLR: A biomarker Bridging systemic inflammation and retinal thrombosis

The NLR, a robust marker of systemic inflammation, has emerged as a shared predictor in both CRVO and BRVO models. Elevated NLR (>2.0) reflects an imbalance between innate (neutrophil-driven) and adaptive (lymphocyte-mediated) immune responses, a dysregulation associated with endothelial dysfunction and prothrombotic states.[21,22] Mechanistically, neutrophils release reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), which contribute to retinal venous endothelial damage, while lymphopenia impairs anti-inflammatory regulation, exacerbating vascular injury.[23,24]

This pro-inflammatory paradigm is supported by histopathological evidence from RVO patients, demonstrating neutrophil infiltration and interleukin-6 (IL-6) upregulation in occluded retinal veins.[25,26] Clinically, the predictive value of NLR extends beyond traditional inflammatory diseases.[27] Moreover, NLR's ability to reflect dynamic immune status provides a significant advantage over static biomarkers such as PD-L1 (an important immune regulatory protein), positioning it as a critical component for real-time risk stratification.[28]

4.2. PDW: platelet activation as a thrombotic driver in CRVO

PDW, a recognized marker of platelet activation, has gained increasing attention in the context of retinal diseases, including DR and arteritic anterior ischemic optic neuropathy (AAION).[29,30] Given that abnormal platelet activation can contribute to thrombosis, PDW has emerged as a significant parameter for predicting the risk of RVO.[31,32] Activated platelets release thromboxane A2 and P-selectin, which promote the formation of retinal venous thrombi.[33] This mechanism is supported by the observation that PDW levels are significantly elevated in CRVO patients compared to controls (14.31% vs. 11.65%, $P < 0.05$).[34] The specificity of PDW for CRVO over BRVO may be attributed to the larger caliber of the central vein, where platelet-rich thrombi are more prevalent.[35] In contrast, BRVO is primarily driven by lipid-induced arteriolar compression,[36] suggesting that PDW may serve as a biomarker specific to CRVO.

4.3. HDL-C: A protective nexus in CRVO pathogenesis

HDL-C was identified as a protective factor against CRVO. Known for its anti-inflammatory, antioxidant, and endothelial-protective properties,[37] HDL-C may reduce the risk of RVO.[38] Beyond its role in lipid transport, HDL-C exerts anti-inflammatory effects by inhibiting the expression of endothelial adhesion molecules, such as VCAM-1.[39] This finding aligns with previous studies demonstrating the protective role of HDL-C in various vascular diseases.[40] Additionally, prior research has incorporated HDL-C into RVO risk prediction models, identifying low HDL-C levels as an independent risk factor for RVO.[16]

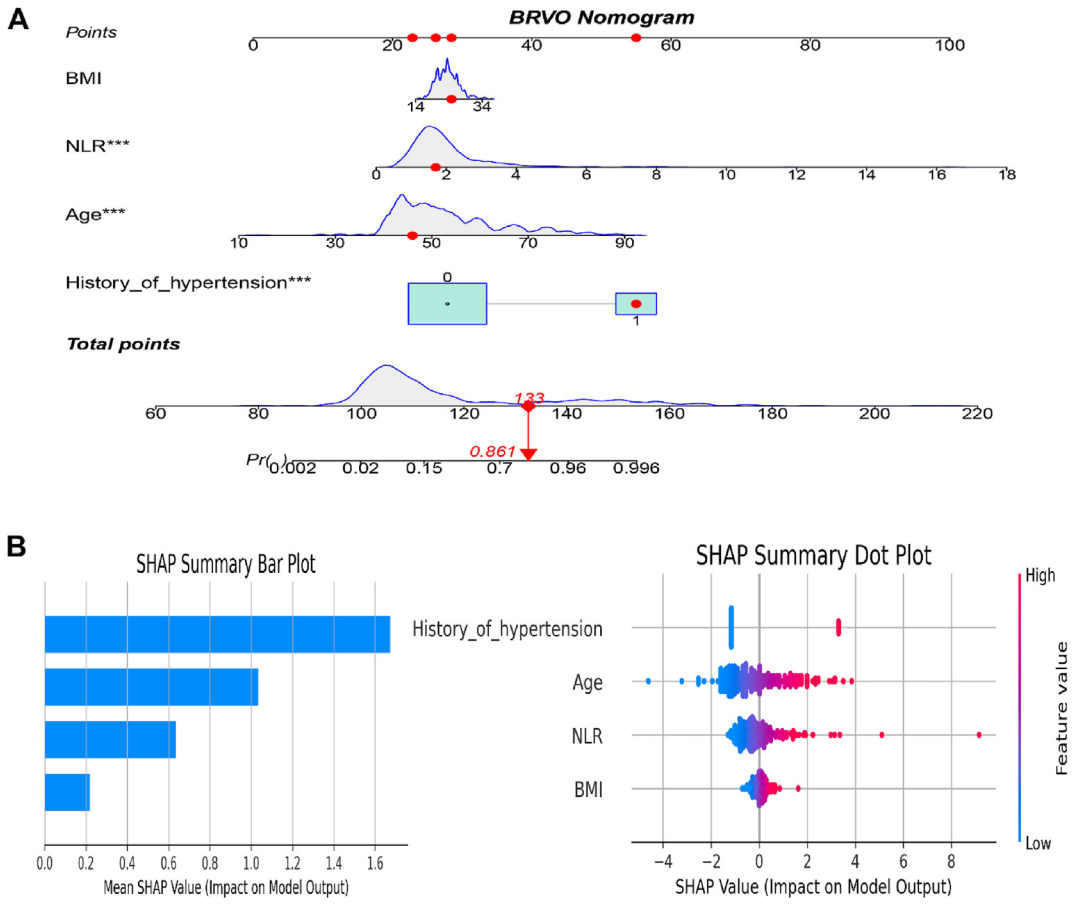

Fig. 4. BRVO-nom Presentation and Interpretation **(A) Dynamic nomogram example**: A 46-year-old with hypertension, BMI = 24.73 kg/m^2, and NLR = 1.7 has an 86.1% BRVO risk. **(B) SHAP-based global interpretation**: The bar chart ranks features by average SHAP value; the dot plot shows increasing BRVO risk with feature changes—red (higher values) and blue (lower values). Vertical stacking indicates value density.

4.4. Systemic diseases: divergent pathways in CRVO vs. BRVO

4.4.1. Diabetes, CAD and cerebral infarction (CRVO)

CRVO is strongly associated with systemic vascular factors.[41] Our study identifies diabetes as a significant risk factor for CRVO, primarily due to its role in vascular complications.[42] Hyperglycemia induces endothelial dysfunction, leading to increased oxidative stress and inflammation, which collectively promote thrombogenesis.[43] Furthermore, DR and associated ischemic changes can exacerbate CRVO risk by disrupting retinal perfusion dynamics.[44]

A population-based study of 15,010 participants revealed that CRVO is linked to age and a family history of stroke, while BRVO is associated with hypertension and atrial fibrillation.[45] The connection between cardiovascular diseases—such as CAD and cerebral infarction—and CRVO highlights the shared pathophysiology of systemic vascular diseases and retinal vascular events.[46,47] These conditions are often driven by atherosclerosis, which impairs blood flow in the retinal veins.[48]

4.4.2. Hypertension (BRVO)

Hypertension, particularly through retinal arteriovenous cross-compression, is a prevalent mechanism underlying BRVO.[36] Elevated systolic blood pressure (SBP) can induce hemodynamic changes that increase venous pressure, thereby raising the risk of occlusion in smaller retinal vein branches.[49] Previous studies have demonstrated that even early-stage hypertension (SBP: 120–129 mmHg) is associated with an increased risk of RVO, with the risk escalating further at higher SBP levels.[50] As a key predictor of BRVO, hypertension contributes to vascular alterations that predispose individuals to RVO by increasing vascular resistance, impairing endothelial function, and causing the narrowing of retinal veins.[51] Additionally, hypertension may promote a hypercoagulable state, exacerbating thrombus formation and worsening pre-existing venous narrowing.[52]

4.5. Age & BMI: metabolic-vascular crosstalk in BRVO

Age and BMI are well-established independent risk factors for BRVO. Advanced age is closely associated with increased vascular stiffness and reduced endothelial function,[53] while elevated BMI, a marker of obesity, is linked to systemic inflammation and metabolic dysregulation.[54] Both factors significantly contribute to an individual's predisposition to BRVO. The relationship between advancing age and BRVO can be attributed to a combination of physiological and pathological changes in the vascular system.[53] With aging, there is a progressive decline in vascular elasticity and an increased tendency for atherogenesis, which can obstruct retinal venous outflow.[55] Older individuals also exhibit a higher prevalence of comorbid conditions such as hypertension, diabetes, and hyperlipidemia.[56] These conditions not only exacerbate venous stasis but also increase the likelihood of thrombus formation within the retinal veins.[55] Furthermore, age-related alterations in the composition of vascular tissues, particularly in collagen and elastin, contribute to increased vessel fragility.[57] This heightened fragility renders older individuals more susceptible to occlusions, further compromising their vascular health.[57]

In addition to age, BMI plays a critical role in the metabolic-vascular interplay that influences RVO risk.[58] Elevated BMI, often indicative of excess body fat, is associated with chronic low-grade inflammation.[54] Adipose tissue secretes pro-inflammatory cytokines that disrupt normal

vascular function, promoting endothelial dysfunction and facilitating thrombus formation.[59] Moreover, obesity is frequently accompanied by insulin resistance and metabolic syndrome, conditions that further impair vascular health and contribute to the pathogenesis of RVO.[60]

4.6. Advancements over existing models

Compared to previous composite RVO models,[12–16] our nomograms introduce several key innovations.

1. Subtype-Specific Biomarker Integration: Incorporation of PDW for CRVO and NLR for both CRVO and BRVO, effectively capturing distinct thrombotic mechanisms.
2. Dynamic Risk Assessment: Implementation of an interactive Shiny calculator (accessible at https://chunlanliang.shinyapps.io/CRVO_Risk/and https://chunlanliang.shinyapps.io/BRVO_Risk/) that facilitates real-time risk stratification, overcoming the static limitations of traditional nomograms.
3. Explainable AI Framework: Integration of SHAP model interpretation, providing transparent visualization of feature contributions and enabling clinically meaningful interpretation of machine learning predictions.

4.7. Limitations and future directions

This study has several limitations. First, it was conducted at a single center with a relatively small sample size and lacked external validation, which may limit the generalizability of the findings. Second, as a retrospective study, it is susceptible to selection bias, and causality cannot be inferred from the results. Third, longitudinal studies are needed to establish causal relationships between the highlighted influencing factors and CRVO/BRVO. Additionally, incorporating multimodal data fusion techniques that integrate clinical, demographic, and imaging data, including optical coherence tomography angiography (OCTA) metrics to assess blood flow dynamics, could enhance future research.

5. Conclusions

In summary, our study successfully developed and validated risk prediction models for CRVO and BRVO, highlighting potential key influencing factors for each subtype. The findings underscore the importance of both traditional cardiovascular risk factors and emerging markers such as NLR and PDW in predicting retinal vein occlusion. Our models demonstrate good predictive performance and clinical utility, potentially aiding healthcare providers in identifying at-risk patients and tailoring preventive strategies. Future studies are encouraged to build on our findings by exploring additional risk factors and validating the models across different populations to enhance their applicability in clinical settings.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki , and the protocol was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (approval number KY-2024-074).

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: CL, LL, JL, JZ; Data collection: CL, WY, QS, JZ; Analysis and interpretation of results: CL, JL; Drafting the manuscript: CL; Review & editing: JL, JZ. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

RVO	Retinal Vein Occlusion
CRVO	Central Retinal Vein Occlusion
BRVO	Branch Retinal Vein Occlusion
AUC	Area Under the receiver operating characteristic Curve
DCA	Decision Curve Analysis
NLR	Neutrophil-to-Lymphocyte Ratio
HDL-C	High-Density Lipoprotein Cholesterol
PDW	Platelet Distribution Width
CAD	Coronary Artery Disease
BMI	Body Mass Index
AIC	Akaike Information Criterion
CI	Confidence Interval
SHAP	Shapley Additive exPlanations
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2025.03.003.

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