• Clinical Research •

Risk factors of non-arteritic anterior ischaemic optic neuropathy and central retinal artery occlusion

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Abstract

● **AIM:** To investigate the difference in risk factors between non-arteritic anterior ischaemic optic neuropathy (NAION) and central retinal artery occlusion (CRAO) and develop a predictive diagnostic nomogram.

● **METHODS:** The study included 37 patients with monocular NAION, 20 with monocular CRAO, and 24 with hypertension. Gender, age, and systemic diseases were recorded. Blood routine, lipids, hemorheology, carotid and brachial artery doppler ultrasound, and echocardiography were collected. The optic disc area, cup area, and cup-to-disc ratio (C/D) of the unaffected eye in the NAION and CRAO group and the right eye in the hypertension group were measured.

● **RESULTS:** The carotid artery intimal medial thickness (C-IMT) of the affected side of the CRAO group was thicker (P=0.039) and its flow-mediated dilation (FMD) was lower (P=0.049) than the NAION group. Compared with hypertension patients, NAION patients had higher whole blood reduced viscosity low-shear (WBRV-L) and erythrocyte aggregation index (EAI; P=0.045, 0.037), and CRAO patients had higher index of rigidity of erythrocyte (IR) and erythrocyte deformation index (EDI; P=0.004, 0.001). The optic cup and the C/D of the NAION group were smaller than the other two groups (P<0.0001). The diagnostic prediction model showed high diagnostic specificity (83.7%) and sensitivity (85.6%), which was highly related to hypertension, the C-IMT of the affected side, FMD, platelet (PLT), EAI, and C/D.

● **CONCLUSION:** CRAO patients show thicker C-IMT and worse endothelial function than NAION. NAION and CRAO may be related to abnormal hemorheology. A small cup and small C/D may be involved in NAION. The diagnostic nomogram can be used to preliminarily identify NAION and CRAO.

● **KEYWORDS:** non-arteritic anterior ischaemic optic neuropathy; central retinal artery occlusion; risk factors; diagnostic prediction model; nomogram

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INTRODUCTION

Non-arteritic anterior ischaemic optic neuropathy (NAION) is a common acute optic nerve damage disease with 2.5-11.8/100 000 incidence in people over 50 years old[1]. Based on existing research findings, common risk factors of NAION include systemic factors such as hypertension, diabetes, hyperlipidemia[2-3], nocturnal arterial hypotension, and obstructive sleep apnea syndrome[4-5]. The anatomical structure of the small optic disc, small cup-to-disc ratio (C/D), small optic cup, or ignoring cup may be local risk factors for NAION[6-7]. In addition to the above risk factors, NAION is also related to drugs and surgery[8-9]. The clinical manifestations of central retinal artery occlusion (CRAO) are similar to those of NAION, usually characterized by sudden and painless vision loss in one or both eyes. NAION and CRAO are fundus ischemic diseases, but their pathogenesis and treatment differ. Most scholars believe that the pathogenesis of NAION originates from acute ischemia of the optic disc caused by non-perfusion or hypoperfusion of the short posterior ciliary artery (SPCA), resulting in ischemia of the optic nerve in the sieve plate front area and sieve plate area[10]. The main treatment of NAION is to improve circulation, reduce optic disc edema and protect the nerve. The onset of CRAO is due to various reasons leading to the interruption of the central retinal artery blood flow, retinal ischemia, hypoxia, and irreversible visual function damage. The treatment of CRAO mainly includes timely and effective recanalization of blood vessels, improvement of circulation, oxygen inhalation, and eye massage. Previous reports have

also confirmed that the two diseases share similar risk factors, such as hypertension, diabetes, and hyperlipidemia[11-13]. Although fundus examination, visual field examination, fundus fluorescein angiography (FFA), and other ophthalmic examinations are helpful for the differential diagnosis of NAION and CRAO. However, for community doctors or family doctors who lack professional ophthalmic examination equipment, facing patients with atypical clinical features, it is difficult to make the correct identification and give timely and effective treatment in a short time. Therefore, if the clinician can find the characteristics or opposite risk factors of the two diseases through comparison and analysis of clinical data and establish a novel diagnostic prediction model displayed as a nomogram to improve the accuracy and practicality in the differential diagnosis of NAION and CRAO, it is extremely important for clinicians to identify and diagnose, and for patients to receive timely and correct treatment.

SUBJECTS AND METHODS

Ethical Approval This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, which approved the waiver of the informed consent application (approval number: [2023]119).

Patients with unilateral NAION diagnosed clinically in the First Affiliated Hospital of Sun Yat-sen University from July 2014 to July 2022 were collected. All patients with NAION presented sudden painless loss of visual acuity in one eye, relative afferent pupillary defect, optic disc edema with or without peripapillary linear hemorrhage, characteristic visual field defects, and early filling defect of the disc by FFA in the affected eye without evidence of other neurological, systemic, or ocular diseases. Patients with a high erythrocyte sedimentation rate or a positive history of giant cell arteritis clinical features were excluded from this study. Totally 37 patients were included in the study, all of whom underwent routine ophthalmic examinations. During the same period, 20 patients with unilateral CRAO diagnosed by FFA and 24 with hypertension diagnosed by internal medicine specialists were enrolled as the control groups. There was no acute visual loss history or impaired visual function at the same period of patient recruitment in the hypertensive control. The unaffected eyes of the NAION group and CRAO group and the right eye of the hypertension group were selected as the study eyes. The gender, age, and systemic disease history of the patients were collected from previous medical records. The data was collected from all study participants during the onset period on various factors including total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, lipoprotein a, red blood cell (RBC) count, platelet (PLT) count, hemoglobin (Hb), hemorheology [whole blood viscosity low-shear, whole blood viscosity middle-shear (WBV-M), whole blood viscosity high-shear (WBV-H), whole blood reduced viscosity high-shear (WBRV-H), whole blood reduced viscosity low-shear (WBRV-L), erythrocyte aggregation index (EAI), index of rigidity of erythrocyte (IR), and erythrocyte deformation index (EDI)]. During the onset period, all participants in the study received a doppler ultrasound of their carotid and brachial arteries using a high-resolution ultrasound machine equipped with a high-frequency linear array ultrasound probe (5-12 MHz, Philips ie33, Netherlands). We collected the carotid artery of the affected side in the NAION and CRAO groups, and the bilateral carotid artery in the hypertension group, for systolic diameter, flow velocity, and intimal medial thickness, and these three variables were averaged for the hypertensive group. The results of flow-mediated dilation (FMD) and carotid artery plaque of every group were recorded. Furthermore, the results of heart valve tests from the echocardiography were collected and recorded for all subjects in the study.

Members of the study collected fundus photos from all subjects using a Canon CR-2 AF digital retinal camera made in Japan. Professional technicians were responsible for capturing these images. Image J 1.60 Software was used to measure the optic disc area, cup area, and C/D of the contralateral unaffected eye of NAION and CRAO and the right eye of the hypertensive patients[14]. To avoid subjective errors, measurements were taken by mixing fundus photographs of the three groups and removing their diagnostic labels. To improve the accuracy of cup measurement, the measurements of cup area and C/D were performed by two independent study members, and inter-observer agreement was analyzed to ensure the accuracy of the assessment.

Statistical Analysis Results were presented as mean±standard deviation (SD) for continuous data and frequency (proportion) for categorical data. When normal distribution was met, continuous data was presented as mean±SD. If not, it was presented as an interquartile range. Continuous variables were compared among the NAION, CRAO, and hypertension groups by one-way ANOVA with Bonferroni correction. In addition, the Chi-square test or Fisher's exact probability method was used to compare the count data among the three groups. Friedman test and Kendall's W test were used to analyze the agreement of two independent observers in the measurement of cup area and C/D. After data cleaning, a single-factor bi-classification logistics regression was used to screen variables, and then a multi-factor bi-classification logistics regression was carried out to construct a nomogram model and visualize it. All statistical analysis was performed in SPSS (Version 25.0, Chicago, USA), and $P<0.05$ was considered statistically significant.

Table 1 Demographic and clinical data of the patients with NAION, CRAO and hypertension *n* (%)

Items	NAION group (*n*=37)	CRAO group (*n*=20)	Hypertension group (*n*=24)	*P*
Age (y, mean±SD)	53.03±7.99	57.95±10.27	58.08±9.25	0.05
Males	26 (70.2)	15 (75)	12 (50)	0.16
Hypertension	22 (59.5)	18 (90)	24 (100)	<0.017[a,c]
Diabetes	4 (10.8)	3 (15)	1 (4.2)	0.5
Hyperlipidemia	12 (32.4)	5 (25)	13 (54.2)	0.1
Cardiac valve disease	12 (32.4)	8 (40)	10 (41.7)	0.73
Coronary heart disease	2 (5.4)	2 (5)	2 (8.3)	0.85
Cerebral stroke	1 (2.7)	5 (25)	0	<0.017[b,c]
Arrhythmia	1	1	0	0.73

NAION: Non-arteritic anterior ischaemic optic neuropathy; CRAO: Central retinal artery occlusion. [a]NAION group *vs* CRAO group; [b]CRAO group *vs* hypertension group. [c]*P*<0.05.

RESULTS

Table 1 summarizes the demographic and clinical data of all study subjects. The NAION group comprised 37 patients, 26 males, and 11 females, with a mean age of 53.03±7.99y. The CRAO group included 15 males and 5 females, with a mean age of 57.95±10.27y, and the hypertension group consisted of 12 males and 12 females, with a mean age of 58.08±9.25y. There were no statistically significant differences in age and gender among the three groups and in the distribution of diabetes, hyperlipidemia, cardiac valve disease, coronary heart disease, and arrhythmia in the three groups. Subgroup analysis revealed that hypertension was more common in the CRAO group than in the NAION group (*P*<0.017) and the incidence of cerebral stroke was higher in the CRAO group than in the hypertension group (*P*<0.017).

There were no statistical differences in total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, lipoprotein a, the incidence of carotid plaque, and the systolic diameter and flow velocity of the common carotid artery on the affected side among the three groups. The carotid artery intimal medial thickness (C-IMT) of the affected side in the CRAO group was thicker than that in the NAION group (*P*=0.039). FMD was higher in the NAION group than in the CRAO group (*P*=0.049) but not significantly different from that in the hypertension group. There were no statistical differences in RBC count, PLT count, and Hb among the three groups. In terms of hemorheology, compared with the hypertension group, the NAION group had higher WBRV-L and EAI (*P*=0.045, 0.037), and the CRAO group had substantially higher IR and EDI (*P*=0.004, 0.001; Table 2).

After the inter-observer agreement analysis of the measurement of cup area and C/D of all subjects by two independent observers, the results showed that Kendall's coefficient of the measurement results of the two independent observers was 0.975, which had strong consistency (*P*<0.001). Table 3 compares the optic disc area, optic cup area, and C/D among the three groups. The results showed no significant difference in optic disc area among the three groups (*P*=0.104). The NAION group had a significantly smaller cup area and C/D than the CRAO and hypertensive groups (*P*<0.0001) while there was no significant difference between the CRAO and hypertensive groups. The proportion of patients with a C/D less than 0.3 was 62.2% in the NAION group and only 10% in the CRAO group. The small C/D proportion in the NAION group significantly differed from that in the other two groups (*P*<0.0001).

Figure 1 illustrates the diagnostic prediction model nomogram based on the following six risk variables which include hypertension, the C-IMT of the affected side, FMD, PLT, EAI, and C/D. As shown in Figure 1, the total point was obtained by adding the points corresponding to the test results of each variable, one total point corresponded to one linear predictor which demonstrated the possibility of the diagnosis of NAION or CRAO. Based on the total score of a patient, the higher the corresponding risk value, the more likely the patient is to be diagnosed was NAION, and vice versa, the more likely the patient is to be diagnosed with CRAO. This diagnostic prediction model can provide clinicians with an intuitive and quantitative tool to predict the probability of NAION or CRAO. The receiver operating curve analysis shows that the area under the curve of the model was 0.93 (Figure 2).

DISCUSSION

Acute autopsy histopathological analysis of NAION patients has never been performed, and animal studies have promoted the study of the underlying disease process of NAION. Still, the pathogenesis of NAION needs to be clarified due to anatomical differences between species[15]. The most common cause of NAION is hypoperfusion or nonperfusion of the optic disc circulation due to the SPCA, which can be caused by various factors[16-17]. When the optic disc capillary perfusion is depressed below the critical autoregulation range, NAION can be triggered in some susceptible individuals. The

Table 2 Comparisons of multiple related factors in the NAION, CRAO and hypertension groups

Variables	NAION group (*n*=37)	CRAO group (*n*=20)	Hypertension group (*n*=24)	*P*
TC [mmol/L, M (IQR)]	5 (4.25, 5.42)	5.21 (4.08, 6.15)	4.6 (3.9, 5.5)	0.49
TG [mmol/L, M (IQR)]	1.38 (1.06, 2.1)	1.79 (1.22, 2.29)	1.26 (0.85, 1.71)	0.113
LDL [mmol/L, M (IQR)]	3.05 (2.59, 3.3)	3.18 (2.59, 4.23)	2.71 (2.26, 3.48)	0.322
HDL [mmol/L, M (IQR)]	1.19 (1.01, 1.41)	1.17 (0.99, 1.37)	1.37 (1.14, 1.53)	0.204
LP-a [mmol/L, M (IQR)]	174 (77.5, 265)	122 (74.5, 245.6)	95 (74.19, 4.25)	0.427
Carotid plaque, *n* (%)	16 (43.2)	12 (60)	14 (58.3)	0.362
Carotid artery flow velocities (cm/s, mean±SD)	80±19.62	81.47±18.94	86.55±15.63	0.39
Carotid artery systolic diameter [mm, M (IQR)]	6.16 (5.91, 7.05)	6.39 (5.97, 6.98)	6.14 (5.56, 6.9)	0.679
C-IMT (mm, M (IQR)]	0.71 (0.64, 0.81)	0.9 (0.7, 1.04)	0.74 (0.65, 0.8)	0.037[a], 0.039[a,c]
FMD (%, M (IQR)]	8.5 (5.3, 11.8)	5.95 (3.88, 8)	7.2 (5.73, 10.3)	0.046[a], 0.049[a,c]
RBC ($\times10^9$/L, mean±SD)	4.86±0.49	4.75±0.4	4.88±0.56	0.623
Hb (g/L, mean±SD)	142.51±19.25	145.87±9.66	139.13±12.19	0.136
PLT ($\times10^9$/L, M [IQR])	260 (219, 305.5)	214.5 (171.75, 266.5)	249.5 (214.25, 294.75)	0.058
WBV-L (mPa·s, mean±SD)	20.23±3.67	17.91±4.23	18.43±3.65	0.056
WBV-M [mPa·s, M (IQR)]	5.22 (4.69, 5.63)	4.95 (4.41, 5.34)	4.74 (4.37, 5.2)	0.235
WBV-H [mPa·s, M (IQR)]	3.92 (3.54, 4.24)	3.75 (3.4, 4.01)	3.65 (3.39, 3,95)	0.412
WBRV-L [mPa·s, M (IQR)]	44.34 (39.35, 47.43)	39.71 (36.86, 44.43)	36.65 (33.36, 46.34)	0.035[a], 0.045[a,d]
WBRV-H [mPa·s, M (IQR)]	5.58 (4.92, 6.29)	5.56 (5.11, 6.2)	4.85 (4.54, 5.96)	0.098
IR, M (IQR)	3.81 (3.41, 4.49)	4.13 (3.77, 4.83)	3.29 (3.04, 4.01)	0.005[b], 0.004[b,e]
EDI, M (IQR)	0.75 (0.71, 0.81)	0.8 (0.75, 0.82)	0.69 (0.67, 0.75)	0.002[b], 0.001[b,e]
EAI, M (IQR)	5.14 (4.89, 5.52)	5.03 (4.67, 5.34)	4.82 (4.54, 5.23)	0.032[a], 0.037[a,d]

NAION: Non-arteritic anterior ischaemic optic neuropathy; CRAO: Central retinal artery occlusion; TC: Total cholesterol; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; LP-a: Lipoprotein a; C-IMT: Carotid artery intimal medial thickness; FMD: Flow-mediated dilation; RBC: Red blood cell; Hb: Hemoglobin; PLT: Platelet; WBV-L: Whole blood viscosity low-shear; WBV-M: Whole blood viscosity middle-shear; WBV-H: Whole blood viscosity high-shear; WBRV-L: Whole blood reduced viscosity low-shear; WBRV-H: Whole blood reduced viscosity high-shear; IR: index of rigidity of erythrocyte; EDI: Erythrocyte deformation index; EAI: Erythrocyte aggregation index; M (IQR): Median (interquartile range). [a]*P*<0.05, [b]*P*<0.01. [c]NAION group *vs* CRAO group, [d]NAION group *vs* hypertension group, [e]CRAO group *vs* hypertension group.

Table 3 Comparisons of optic disc parameters in the NAION, CRAO and hypertension groups

Optic disc parameters	NAION group (*n*=37)	CRAO group (*n*=20)	Hypertension group (*n*=24)	*P*
Optic disc area (mm^2 mean±SD)	1.45±0.29	1.61±0.32	1.44±0.26	0.104
Optic cup area [mm^2, M (IQR)]	0.13 (0.042, 0.21)	0.33 (0.23, 0.37)	0.3 (0.25, 0.39)	<0.0001[a]
C/D, M (IQR)	0.26 (0.13, 0.34)	0.36 (0.31, 0.4)	0.37 (0.33, 0.44)	<0.0001[a]
C/D<0.3, *n* (%)	23 (62.2)	2 (10)	0	<0.0001[a]

NAION: Non-arteritic anterior ischaemic optic neuropathy; CRAO: Central retinal artery occlusion; C/D: Cup-to-disc ratio; M (IQR): Median (interquartile range). [a]*P*<0.01.

severity and extent of optic nerve damage caused by transient hypoperfusion or nonperfusion are generally less than that of obstructive vascular disorders such as CRAO. Studies have shown that 41% of eyes show spontaneous visual improvement in NAION[18], whereas only 22% show improvement in CRAO[19]. In previous studies, the risk factors of NAION and CRAO are relatively similar, but studies on the differences between the risk factors of the two diseases are rare.

This study showed no significant difference in the distribution of diabetes, hyperlipidemia, cardiac valve disease, coronary heart disease, and arrhythmia between NAION and CRAO patients, whereas hypertension was more common in CRAO patients. Schmidt *et al*[20] found that 79.8% of patients with bilateral CRAO had hypertension, and 78.9% of patients with unilateral CRAO had hypertension. Hayreh[21] believes that the stimulation of long-term hypertension leads to increased vascular wall tension, decreased autoregulation ability, decreased reactive relaxation ability of the SPCA, and inability to obtain normal blood perfusion. NAION is primarily a hypoperfusion disease and can only be triggered when hypertension affects vascular regulation beyond the range of the automatic law of the optic disc. In this study, the CRAO group had a higher incidence of cerebral stroke than the hypertension group, which is consistent with previous research

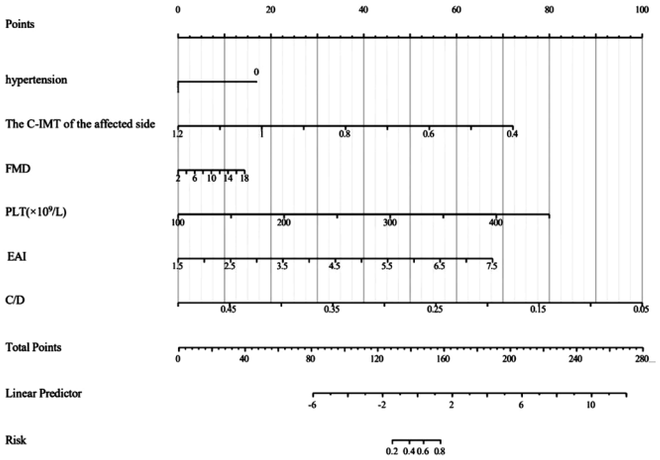

Figure 1 Nomogram C-IMT: Carotid artery intimal medial thickness; PLT: Platelet; EAI: Erythrocyte aggregation index; C/D: Cup-to-disc ratio; Points: Single score corresponding to each predictive variable under different values; Total points: Total score of the individual scores corresponding to the values of all variables; Linear predictor: Linear predictive value; Risk: Probability of a diagnosis of non-arteritic anterior ischaemic optic neuropathy (NAION) or central retinal artery occlusion (CRAO).

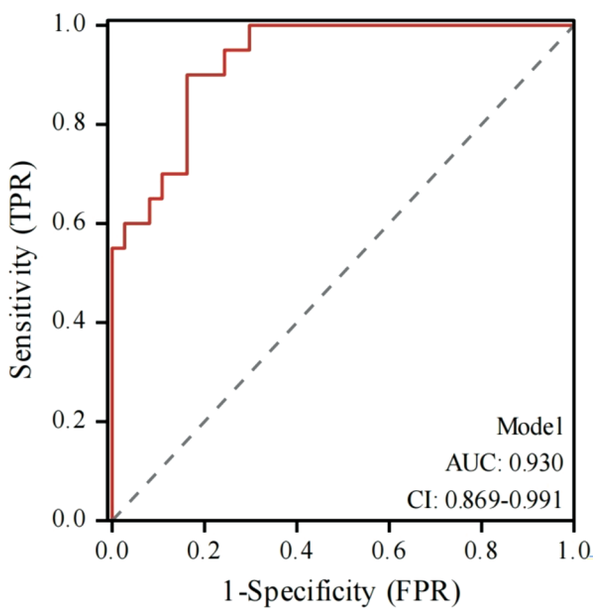

Figure 2 Receiver operator characteristic curve The area under the curve of the model is 0.93, CI (0.869-0.991). CI: Confidence interval; AUC: Area under curve; FPR: False positive rate; TPR: True positive rate.

results. Lavin *et al*[22] found that 37.3% of CRAO patients had concurrent ischemic stroke in their systematic screening of risk factors. One study found that symptomatic ischemic stroke, transient ischemic attack, and amaurosis frequently occur before, during, or after CRAO[23]. Stroke patients are prone to CRAO, the reason may be that the internal carotid artery system is one of the components of the cerebral artery system, the ophthalmic artery is a branch of the internal carotid artery, and the central retinal artery is a branch of the ophthalmic artery. Therefore, the occurrence of cerebrovascular diseases may involve the central retinal artery.

C-IMT is a well-recognized marker of atherosclerosis and a significant predictor of cardiovascular events. Previous studies have shown that C-IMT on the affected side of NAION patients is significantly increased compared with healthy controls[24], and it has been found that C-IMT and carotid plaque score are related to NAION with hypertension, suggesting that NAION may be related to carotid atherosclerosis[25]. The study showed that C-IMT in NAION patients was not significantly different from that in the hypertensive group. This may be due to the vascular endothelial damage in hypertensive patients, leading to the thickening of C-IMT and narrowing of the carotid, and the formation of atherosclerotic plaques. Dropiński *et al*[26] found that the C-IMT of CRAO patients was thicker than the average population. Hayreh *et al*[27] also confirmed that CRAO was an embolic disease, and the primary source of embolism was a carotid atherosclerotic plaque. The results of this study showed that the thickness of C-IMT in the CRAO group was greater than that in the NAION group, which indirectly indicated that the occurrence of CRAO may be more closely related to the thickening of C-IMT than that of NAION.

Yao *et al*[28] evaluated systemic vascular endothelial function using noninvasive physiological methods to measure FMD in NAION patients. They found that FMD in NAION was significantly lower than in hypertensive and regular groups, possibly related to systemic vascular endothelial dysfunction. In this study, there was no significant difference in FMD between the NAION group and the hypertensive group, which was inconsistent with the results of Yao *et al*[28], and it may be that the hypertensive group in their study took antihypertensive medicine and improved vascular endothelial function[29]. However, due to the limited sample size, this study could not separate the effects of hypertension and hypertensive drugs on endothelial function. There are few studies on CRAO and FMD. Dropiński *et al*[26] studied the relationship between CRAO and FMD for the first time. They found that the FMD of CRAO patients was lower than that of the control group, suggesting that CRAO is related to vascular endothelial damage. The study is the first to compare FMD between CRAO and NAION, showing that FMD in the CRAO group is lower than in the NAION group. In the pathogenesis of NAION, endothelial dysfunction can affect vascular tone, leading to an imbalance between vascular contraction and relaxation, significantly impairing the function of endothelium-derived relaxant factors and resulting in hypoperfusion of the SPCA. One study has shown low-grade systemic inflammation in CRAO patients, proposing that CRAO may occur in a proinflammatory context[30]. The endothelium controls the coagulation process by secreting various regulatory substances, and endothelial injury may cause a pro-inflammatory and pro-

coagulation state, change blood composition and viscosity, and quickly lead to thrombosis. Endothelial dysfunction may be involved in the pathogenesis of the two diseases and the pathogenesis may differ. The severity of endothelial dysfunction in CRAO patients may be greater than in NAION patients. Further studies are needed to assess the pathogenic risk and prognosis of FMD in the two diseases.

Hemorheology can assess the flow and velocity of the blood. Abnormal hemorheology may lead to pathological changes in systemic tissue and organ blood perfusion or coagulation cascade abnormalities, resulting in various microcirculation disorders. This study found that the WBRV-L and EAI of NAION patients were higher than those of the hypertension group, consistent with the research of Wang *et al*[31]. In addition, Brooks and Seaman[32] confirmed that the blood viscosity measured at a low shear rate reflects the aggregation degree of RBC. The higher the aggregation degree of RBC, the higher the blood viscosity at a low shear rate. Both WBRV-L and EAI in the NAION group were higher than those in the hypertension group, indicating that blood viscosity was increased in NAION patients. Increased blood viscosity and increased blood flow resistance lead to hypoperfusion of the SPCA. At the same time, blood cells gather to form numerous tiny thrombi in microcirculation, which may be the cause of optic disc ischemia. Several studies have shown that increased blood viscosity and decreased erythrocyte deformability are found in obstructive vascular diseases[33-34]. This study found that the IR and EDI of the CRAO group were higher than those of the hypertension group. IR and EDI are essential factors in determining blood flow resistance and reflect blood viscosity to some extent. Endothelial cells play a vital role in the regulation of blood viscosity. Under physiological conditions, endothelial cells, as sensors of blood viscosity, secrete various vascular factors to regulate vascular tension and reduce blood viscosity by improving RBC deformability, reducing RBC aggregation, and inhibiting PLT aggregation and adhesion[35-37]. An abnormal increase in blood viscosity under pathological conditions can directly or indirectly lead to endothelial dysfunction. Endothelial cell anti-thrombosis and anti-adhesion function fail, and blood viscosity further increases, forming a vicious circle with endothelial dysfunction, leading to thrombosis and CRAO.

The “high-risk optic disc” plays a vital role in the pathogenesis of NAION. Small scleral trenches and small openings in the Bruch membrane can result in minor or ignoring cups. In individuals with small or blind cups, nerve fibers produce a “crowding phenomenon” as they pass through the limited space at the optic papilla and scleral sieve plate. Under the action of certain factors such as hypertension and arteriosclerosis, the ability of blood vessels to regulate themselves is reduced. When the nutrient arteries of the optic nerve are hypoperfused due to nocturnal hypotension or others, the optic nerve is ischemia, the axoplasm flow is stagnant, and the swollen axons compress the capillaries between the optic nerve fiber bundles in a limited space. The optic nerve ischemia is further aggravated. Eventually, a vicious cycle of ischemia-edema-ischemia is formed, resulting in NAION. Many studies have found that the anatomical structure with a small cup or ignoring cup or small C/D is more common in NAION patients[6-7]. The study further compared the optic disc parameters of NAION, CRAO, and hypertensive groups. The NAION group had a significantly smaller cup area and C/D than the CRAO and hypertensive groups. However, there was no significant difference in cup area and C/D between the CRAO and hypertensive groups. It is suggested that individuals with a small C/D are more likely to develop NAION when they have some vascular risk factors. With the progress of research, optic disc drusen is an independent risk factor for NAION, and optic disc drusen has been found in some young NAION patients without vascular risk factors[38]. Optic disc drusen tend to occur in crowded optic discs with small scleral canals, which may constitute the basis of NAION[39]. The presence of optic disc drusen aggravates the crowding between optic nerve fiber bundles and the axon swellings. At the same time, the optic disc drusen directly compress the capillaries of the optic nerve, which further aggravates ischemia and causes NAION. The incidence of bilateral optic disc drusen in young NAION patients is as high as 95.2%. It is hypothesized that patients with bilateral drusen are more likely to have larger or faster-growing optic disc drusen in each eye, thus increasing the risk of NAION[40]. Therefore, the correlation between the size, morphology, or location of optic disc drusen and the incidence of NAION may become a new research direction.

For some community hospitals or family doctors who lack comprehensive ophthalmic examination equipment, there is a great need to devise clinical prediction models based on demographic characteristics, clinical manifestations, and common laboratory results to help guide clinicians in distinguishing between NAION and CRAO, reduce the misdiagnosis rate, reduce the diagnosis time of patients, and enable patients to receive timely treatment. However, to our knowledge, there have been few relevant research reports on this topic. This is the first time that a diagnostic prediction model combining risk factors for NAION and CRAO has been used to rapidly differentiate these two diseases. The intuitive, easy-to-use characteristics of the nomogram will facilitate its wide application. As shown in Figure 1, the point of each variable can be easily acquired and after calculating the total points of the 6 variables, the possibility of diagnosing a patient as having NAION or CRAO was intuitively demonstrated.

There are some limitations to the present study. One is that this study did not include all common risk factors associated with NAION and CRAO. Second, a comprehensive assessment of the cardiovascular system in these patients was not performed in this study. We hope to improve the related examinations of the cardiovascular system and comprehensively evaluate the function of the cardiovascular system in future studies. Third, this study is a single-center study based on a hospital. Not enough patients were included in this research. Due to the limited sample size, the power of this prediction model could not be verified. In the future, the effectiveness of the model will be better validated if prospective research can be carried out in multiple centers. At the same time, the inclusion of more variables in the screening may help build a better prediction model for distinguishing and diagnosing NAION and CRAO.

In conclusion, this study showed that hypertension was more common in CRAO patients than in NAION patients and cerebral stroke may be one of the risk factors for CRAO. The thickness of C-IMT and the severity of endothelial dysfunction in CRAO patients are more significant than in NAION patients. WBRV-L and EAI may be related to NAION, while IR and EDI may be associated with CRAO. Small C/D and small optic cup may play an essential role in the pathogenesis of NAION, and such optic disc structures may not be associated with CRAO. The diagnostic nomogram based on the retrospective study is a practical tool to differentiate between NAION and CRAO.

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