

The Association Between Fundus Changes and Visual Prognosis in Central Retinal Artery Occlusion

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Purpose: To study the association between fundus changes and visual prognosis in central retinal artery occlusion (CRAO).

Methods: A total of 222 CRAO cases hospitalized at Hebei Eye Hospital between January 2013 and December 2016 were included in this study. Fundus photographs on admission were evaluated via dual independent image review. Retinal ischemic edema and cilioretinal arteries were graded. Logistic regression analysis was performed to explore the association between fundus findings and visual prognosis in CRAO.

Results: The main fundus changes in CRAO patients on admission included retinal ischemic edema (95.0%), cherry-red spot (89.6%), retinal arterial narrowing (65.3%) and venous narrowing (53.6%), cotton-wool spots (53.6%), optic disc margin blurring (36.0%) and pallor (35.1%), retinal venous dilation (21.2%), and retinal hemorrhages (12.6%). Upon admission, retinal edema grades were grade 0 in 11 eyes (5.0%), grade 1 in 23 (10.4%), grade 2 in 80 (36.0%); and grade 3 in 108 (48.6%). Forty-seven eyes (21.1%) showed fissure-like edema, while 164 eyes (73.9%) exhibited a diffuse pattern. Chi square test showed the grade and pattern of retinal ischemic edema, the border and size of the cherry-red spot, the presence of retinal hemorrhage and cotton wool spots, macular folds and retinal arterial narrowing were all significantly associated with the time from symptom onset to presentation. Multivariate logistic regression analysis identified visual acuity at presentation, retinal ischemic grade, optic disc margin clarity, cherry-red spot size, and the presence of a cilioretinal artery supplying the macula as predictive factors for visual prognosis in CRAO.

Conclusion: The fundus changes in acute CRAO were correlated with the visual prognosis. Visual acuity at presentation, grade of retinal ischemic edema, clarity of the optic disc margin, size of the cherry-red spot, and the presence of a cilioretinal artery supplying the macula could be predictive factors for visual prognosis in CRAO.

Keywords: central retinal artery occlusion, visual prognosis, retinal ischemic edema, cherry red spot, vascular change, predictive factor

Introduction

Central retinal artery occlusion (CRAO) is an ophthalmic emergency. Approximately 90% of patients present with visual acuity (VA) worse than 20/200.¹⁻⁴ A variety of therapeutic interventions are employed for CRAO, including ocular massage, intraocular pressure reduction, vasodilation, oxygen therapy, thrombolysis et al. However, none of these treatments has been validated to improve the visual prognosis of CRAO. In existing literature, once the sample size is statistically sufficient, consistently about 20%-40% of CRAO eyes ultimately achieve a VA of 20/200 or better.⁵⁻⁹ Even

CRAO eyes without treatment or with only ocular massage achieved a VA of 20/200 or better in 29% of cases.² Current literature suggests that VA in a subset of CRAO eyes might improve either spontaneously or following treatment, whereas another subset could suffer severe visual impairment despite undergoing the most aggressive interventions administered immediately after symptom onset. Distinguishing patients with distinct visual prognoses is of great importance. Current clinical studies on CRAO treatment often impose restrictions on the time between symptom onset and presentation, but overlook the distinction of patients with different visual prognosis. This could be one of the contributing factors underlying the failure of some clinical trials or the inconsistent conclusions across studies.

Research on predicting visual prognosis in CRAO is limited. Hayreh suggested that the factors influencing visual outcome include the duration of acute retinal ischemia, the cause and type of CRAO, the site of occlusion, and the presence and area of supply by a cilioretinal artery.¹⁰ Several other studies showed associations between visual prognosis and the type of CRAO,^{11,12} changes in fluorescein angiography,^{11,12} alterations in optical coherence tomography (OCT),^{13–16} and the “spot sign” in B-scan ultrasound.^{17–19} Fundus color photography is now one of the most fundamental ophthalmic examinations, providing an objective record of fundus changes. It allows for convenient and intuitive image evaluation, and the capability to magnify images dozens of times on a screen reveals subtle fundus changes with great clarity. This study aims to study the association between fundus changes and visual prognosis in CRAO and to investigate predictive factors for visual prognosis.

Methods

Study Design and Participants

This retrospective study was conducted at Hebei eye Hospital, Hebei Province, China. The medical records of inpatients diagnosed with CRAO between January 2013 and December 2016 were reviewed. CRAO was diagnosed via characteristic clinical features including sudden visual loss in one eye, ischemic retinal whitening, cherry-red spot in the macula, delayed filling of the retinal vessels and prolonged retinal arteriovenous circulation on fundus fluorescein angiography (FFA), thickening and hyperreflectivity in inner retina layers in optical coherence tomography (OCT). Patients with other ocular diseases such as retinal vein occlusion, macular degeneration, glaucoma, optic neuropathy, proliferative diabetic retinopathy were excluded. A total of 252 consecutive CRAO patients were screened; 222 had clear 45° posterior pole color photographs and were included in this study. All participants received conservative treatment, including oxygen therapy, sublingual nitroglycerin, retrobulbar atropine injection, intravenous vasodilators, and oral aspirin. Demographic data, medical histories, best corrected visual acuity (BCVA), ocular findings, treatment regimens, and clinical courses were collected. The final VA was defined as the BCVA at the last follow-up. All patient data were de-identified and anonymized prior to analysis to ensure confidentiality.

Fundus color photographs upon admission were performed by Topcon TRC-NW6S. Two ophthalmologists (HW/RY) experienced in retinal diseases independently evaluated the fundus photographs of enrolled CRAO patients. The inter-rater and intra-rater reliability was quantified, with all Kappa coefficients (for categorical variables) and intraclass correlation coefficients (for continuous variables) between 0.6 to 0.95. When interpretation discrepancies arose, a senior attending physician (MLZ) served as the final arbitrator. To evaluate the severity of retinal ischemic edema, we established a grading system for edema based on representative reference images derived from a large series of CRAO fundus photographs. Grading was performed by comparing the CRAO fundus photograph with these reference images.

Retinal ischemic edema was graded as (see [Figure 1](#)):

Grade 0: No macular opacity, the retina appears clear and translucent;

Grade 1: Mild macular edema, the retina is slight haze, resembling a thin mist obscuring retinal details;

Grade 2: Medium macular opacity, the retina presents diffuse haze, through which the orange-tinted choroidal background remains partially visible.

Grade 3: Severe macular opacity, where the macular and perimacular areas exhibit whitish-gray opacity, completely obscuring the underlying orange choroidal background.

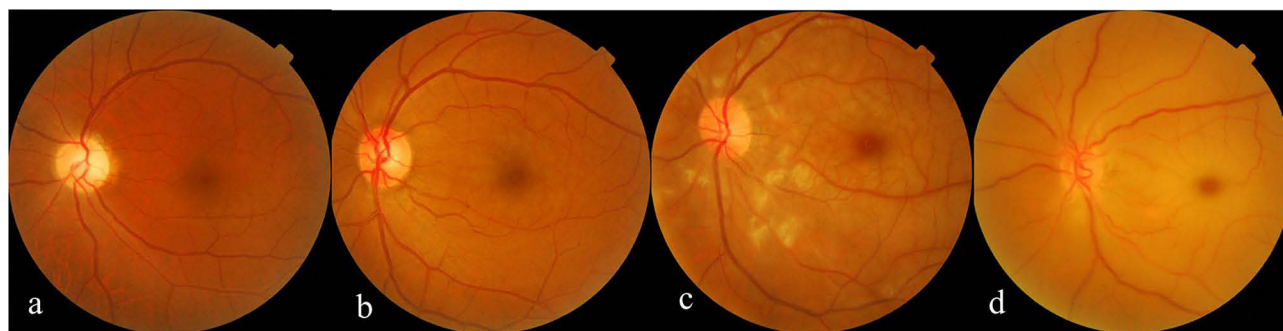


Figure 1 Reference images of retinal ischemic edema. (a) Grade 0: No macular opacity, the retina appears clear and translucent; (b) Grade 1: Mild macular edema, the retina is slight haze, resembling a thin mist obscuring retinal details; (c) Grade 2: Medium macular opacity, the retina presents diffuse haze, through which the Orange-tinted choroidal background remains partially visible; (d) Grade 3: Severe macular opacity, where the macular and perimacular areas exhibit whitish-gray opacity, completely obscuring the underlying orange choroidal background.

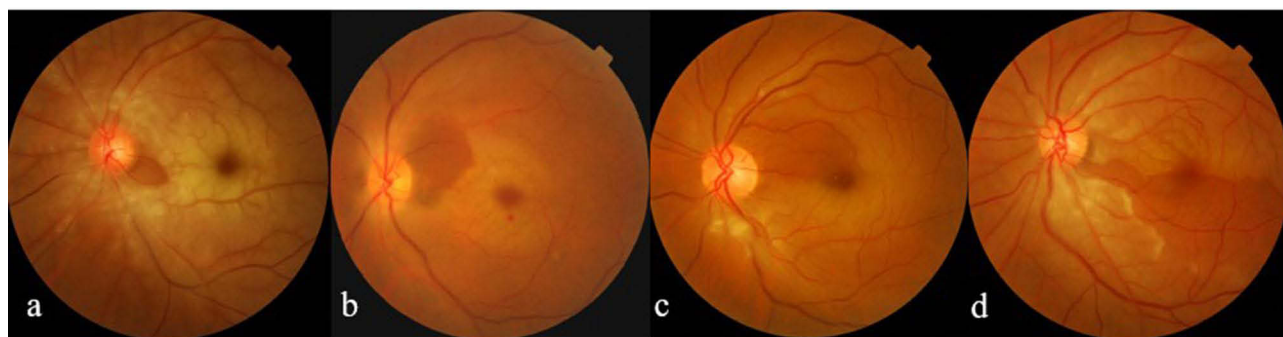


Figure 2 Grading of cilioretinal artery. (a) Grade 1: Perfusion territory ≤ 1 disc area (DA); (b) Grade 2: Perfusion territory between Grades 1 and 3; (c) Grade 3: Perfusion extends nasal to the fovea, supplying retina nasal to the fovea without reaching temporal fovea; (d) Grade 4: Perfusion extends to or beyond the temporal side of the fovea.

Cilioretinal artery may affect visual acuity in eyes with CRAO. Therefore, we grade cilioretinal artery by its perfusion territory area (see Figure 2).

Grade 1: Perfusion territory ≤ 1 disc area (DA).

Grade 2: Perfusion territory between Grade 1 and 3.

Grade 3: Perfusion extends nasal to the fovea, supplying retina nasal to the fovea without reaching temporal fovea.

Grade 4: Perfusion extends to or beyond the temporal side of the fovea.

Statistical Analysis

Clinical data of CRAO patients was input into computer using Epidata 3.1 software. Statistical analyses were performed using SPSS 18.0. Fundus changes in the CRAO eyes with final VA $< 20/200$ were compared against those in eyes with final VA $\geq 20/200$. Categorical variables were described using frequencies and percentages, and compared using Pearson's chi-square test or Fisher's exact test. Continuous variables were presented as mean \pm standard deviation or median, and compared using the *t*-test or Mann-Whitney *U*-test. A two-sided *p*-value of < 0.05 was considered statistically significant.

Binary logistic regression analysis was performed to investigate the relationship between fundus changes and visual prognosis in CRAO and to identify predictive factors for visual outcome. To ensure a more homogeneous sample, cases were excluded if they met either of the following criteria: (1) symptom onset exceeded 1 week, or (2) hospitalization duration was < 1 week (except for patients with a BCVA $\geq 20/60$ at discharge). The dependent variable was defined as follows: $Y = 0$ for a final BCVA ≥ 0.1 , and $Y = 1$ for a final BCVA < 0.1 . Predictor variables with a significance of $p < 0.05$ from univariate analyses were entered into the multivariate logistic regression model to identify independent factors associated with the visual prognosis.

Results

Demographic data, medical histories, visual acuity, interval between symptom onset and admission, follow-up time of the 222 participants were shown in Table 1.

Fundus Changes in CRAO

The principal fundus findings at presentation in CRAO included retinal ischemic edema, cherry-red spot, retinal arterial/venous narrowing, and the optic disc margin blurring. Additional changes may be present but these constitute the core features (see Table 2).

Optic Disc Changes in CRAO

Upon presentation, optic disc changes were observed in 125 of 222 eyes (56.3%), primarily manifesting as disc pallor and disc margin blurring. Disc pallor was present in 78 eyes (35.1%). Disc pallor should not be interpreted as optic nerve atrophy; the pallor reflects optic disc hypoperfusion with a diminished reddish hue compared with the fellow normal eye (see Figure 3a and b). Disc margin blurring occurred in 80 eyes (36.0), accompanied by notable peripapillary retinal whitish edema without elevation of the optic disc or the surrounding retina. In some cases, the disc-margin blur was concentrated at the superior and inferior parts, with relatively distinct nasal and temporal margins. The concomitant presence of disc pallor and margin blurring was observed in 33 eyes (14.9%) (see Figure 3c and d).

Vascular Changes in CRAO

Upon admission, retinal vascular alterations were present in 181 eyes (81.5%), of which 145 eyes (65.3%) exhibited retinal arterial narrowing (See Figure 3e) and 119 eyes (53.6%) showed retinal venous narrowing. Approximately half of the CRAO eyes had concurrent arterial and venous narrowing (110/222, 49.5%) (See Figure 3b, d and f). Retinal vascular narrowing was most readily observed in the large branch vessels of the peripapillary region and those located superior and inferior to the macula. Affected vessels demonstrated not only a reduction in diameter but also irregularities in caliber. Retinal venous dilation, a frequently overlooked sign in CRAO, was present in 47 eyes (21.2%) in this cohort. The dilation was characterized by an increase in venous diameter and a reduced tapering of the lumen upon successive branching compared to normal retinal veins (see Figure 3c and e). Both retinal venous narrowing and dilation were

Table 1 Demographic and Clinical Characteristics of the 222 CRAO Participants

		Overall (n=222)	Final BCVA		p value
			<20/200 (n=129)	≥20/200 (n=93)	
Gender (n, %)	Male	156 (70.3)	98 (76.0)	58 (62.4)	0.029
	Female	66 (29.7)	31 (24.0)	35 (37.6)	
Age (n, %)	≤45	38 (17.1)	21 (16.3)	17 (18.3)	0.881
	45-60	87 (39.2)	50 (38.8)	37 (39.8)	
	>60	97 (43.7)	58 (45.0)	39 (41.9)	
History (n, %)	Hypertension	156 (70.3)	92 (71.3)	64 (68.8)	0.688
	Diabetes	20 (9.0)	7 (5.4)	13 (14.0)	0.28
	CHD	19 (8.6)	14 (10.9)	5 (5.4)	0.150
	CVD	36 (16.2)	25 (19.4)	11 (11.8)	0.132
Interval between symptom onset and admission (n, %)	≤24h	92 (41.4)	57 (44.2)	35 (37.6)	0.658
	24h-72h	52 (23.4)	31 (24.0)	21 (22.6)	
	72h-1w	48 (21.6)	25 (19.4)	23 (24.7)	
	>1w	30 (13.5)	16 (12.4)	14 (15.1)	
Smoking (n, %)	Yes	101 (45.5)	65 (50.5)	36 (38.7)	0.085
Drinking (n, %)	Yes	79 (35.6)	52 (40.3)	27 (29.0)	0.083
Baseline BCVA (n, %)	≤FC	154 (69.4)	115 (89.1)	39 (41.9)	< 0.001
	>FC	68 (30.6)	14 (10.9)	54 (58.1)	
Follow-up duration (M±SD, day)		16.0±8.1	15.0±7.1	17.5±9.3	0.022

Abbreviations: BCVA, best corrected visual acuity; CHD, coronary heart disease; CVD, cerebrovascular disease; FC, finger counting.

Table 2 Fundus Changes in CRAO

		Overall (n=222)	Final BCVA		p value
			<20/200 (n=129)	≥20/200 (n=93)	
Optic disc (n, %)	Normal	97 (43.7)	43 (33.3)	54 (58.1)	< 0.001
	Disc palor	78 (35.1)	51 (39.5)	27 (29.0)	0.106
	Margin blurring	80 (36.0)	62 (48.1)	18 (19.4)	< 0.001
Vascular Change (n, %)	Arterial narrowing	145 (65.3)	88 (68.2)	57 (61.3)	0.285
	Venous narrowing	119 (53.6)	77 (59.7)	42 (45.2)	0.032
	Venous dilation	47 (21.2)	21 (16.3)	26 (28.0)	0.036
	Intravascular emboli	5 (2.3)	4 (3.1)	1 (1.1)	0.316
	Flow interruption	12 (5.4)	9 (7.0)	3 (3.2)	0.223
	Vascular sheathing	10 (4.5)	8 (6.2)	2 (2.2)	0.151
	Cilioretinal artery (n, %)	Yes	69 (31.1)	35 (27.1)	34 (36.6)
No (Grade 0)		153 (68.9)	94 (72.9)	59 (63.4)	
Grade 1		21 (9.5)	15 (11.6)	6 (6.5)	
Grade 2		23 (10.4)	15 (11.6)	8 (8.6)	
Grade 3		11 (5.0)	3 (2.3)	8 (8.6)	
Grade 4		14 (6.3)	2 (1.6)	12 (12.9)	0.001
Retinal Changes (n, %)	Ischemic edema	211 (95.0)	124 (96.1)	87 (93.5)	0.383
	Grade 0	11 (5.0)	5 (3.9)	6 (6.5)	
	Grade 1	23 (10.4)	6 (4.7)	17 (18.3)	
	Grade 2	80 (36.0)	42 (32.6)	38 (40.9)	
	Grade 3	108 (48.6)	76 (58.9)	32 (34.4)	< 0.001
	Diffused edema*	164 (77.3)	99 (76.7)	65 (70.0)	
	Fissure-like edema*	47 (21.7)	25 (19.4)	22 (23.7)	0.378
Cherry-red spot (n, %)	Macular fold	34 (15.3)	29 (22.5)	5 (5.4)	< 0.001
	Yes	199 (89.6)	119 (92.2)	80 (86.0)	
	Well-defined	32 (16.1)	23 (19.3)	9 (11.3)	0.128
	< 1/3 disc diameter	61 (30.7)	52 (43.7)	9 (11.3)	< 0.001
Cotton-wool spot (n, %)	Yes	119 (53.6)	66 (51.2)	53 (57.0)	0.390
Hemorrhage (n, %)	Yes	28 (12.6)	12 (9.3)	16 (17.2)	0.080

Note: *Totally 211 eyes showed retinal ischemic edema.

correlated with the final visual outcome ($\chi^2=4.587$, $p=0.032$; $\chi^2=4.416$, $p=0.036$). Eyes with venous narrowing had a poorer visual prognosis, whereas those exhibiting venous dilation were associated with a more favorable visual outcome. Other vessel-associated changes, such as intravascular emboli, vascular flow interruption (see [Figure 3d](#)), and vascular sheathing, were less frequently encountered in this case series (see [Table 2](#)).

A cilioretinal artery was present in 69 eyes (31.1%) in this case series, all of which arose from the temporal side of the optic disc. The majority of the cilioretinal arteries supplied the papillomacular bundle or the areas immediately above and below it. Twenty-five eyes (25/69, 36.2%) had patent cilioretinal arteries reaching or even extending temporal to the macula. The cilioretinal arteries were graded into four levels according to the area they supplied (see [Figure 2](#)). The grade of the cilioretinal artery showed a significant correlation with visual outcome ($\chi^2 = 18.046$, $p = 0.001$; see [Table 2](#)).

Retinal Changes in CRAO

The pathological changes secondary to acute ischemia and hypoxia represent the most direct evidence for diagnosing CRAO. Retinal alterations induced by CRAO included retinal ischemic edema, cherry-red spot, cotton-wool spots, and retinal hemorrhages, among others.

Retinal whitish edema secondary to acute ischemia was the most prominent fundoscopic finding in CRAO. Among the patients in this series, varying degrees of retinal whitish edema were observed in 211 eyes (95.0%), while 11 eyes (5.0%) showed no retinal edema at presentation (see [Table 2](#)). The retinal ischemic edema caused by CRAO was predominantly located in the posterior pole, particularly involving the macula and the surrounding retina. The edema

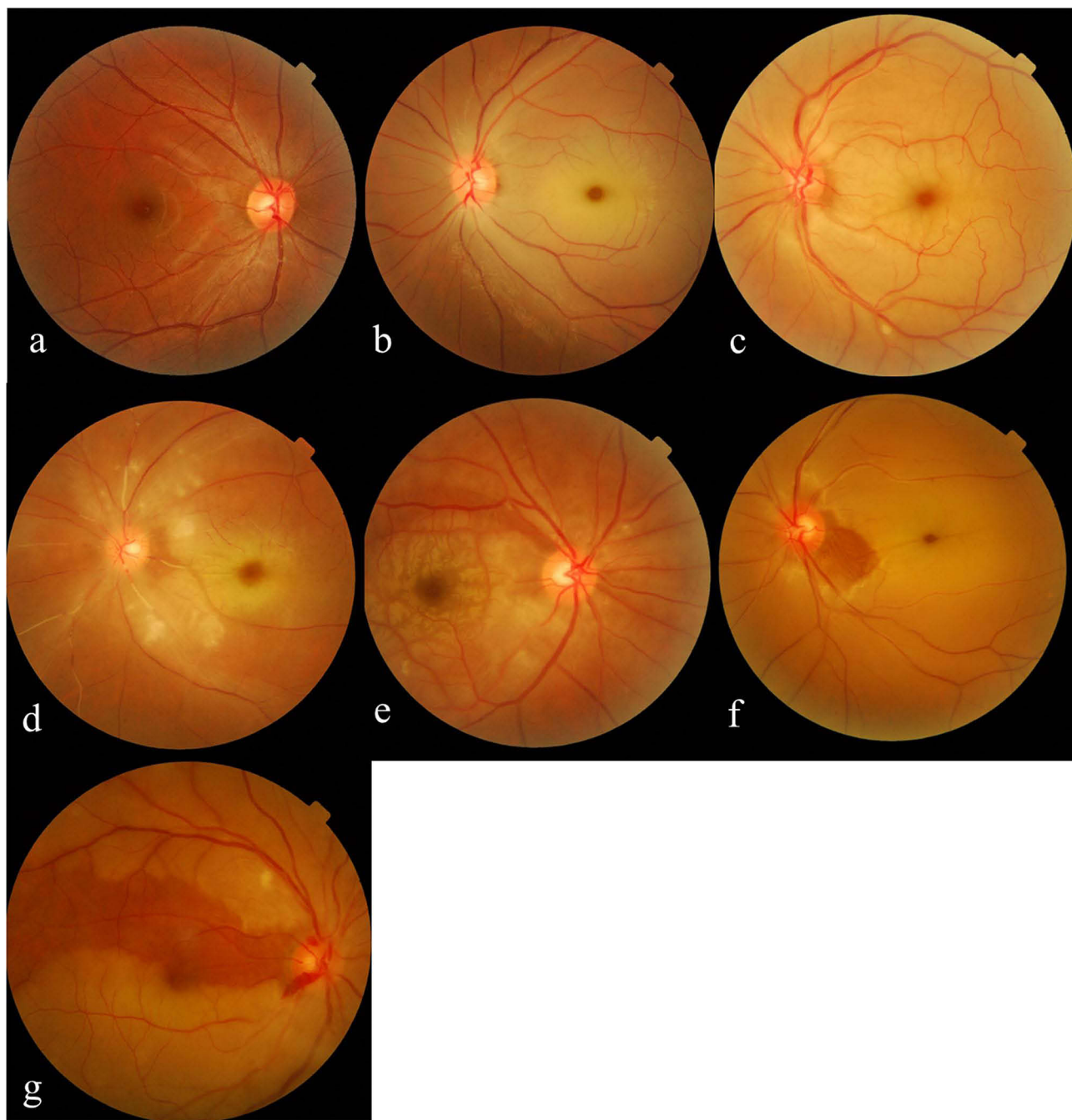


Figure 3 Fundus findings of CRAO. (a) Normal fundus; (b) Disc pallor, arterial and venous narrowing, macular diffused edema, well-defined and punched-out cherry red spot; (c) Disc palor and margin blurring, retinal arterial narrowing and venous dilation; (d) Disc pallor, margin blurring, vascular flow interruption and cotton-wool spots; (e) Macular fissure-like edema, dilated retinal vein, and cherry red spot with indistinct border; (f) Diffused macular edema with folds; (g) Hemorrhage on the surface of disc adjacent to the cilioretinal artery.

appeared as a diffuse whitish opacity in the majority of affected eyes (see [Figure 3b](#) and [f](#)); however, in 22.3% (47/211) of eyes, a relatively normal-colored narrow band was preserved along the retinal arteries, resulting in a “fissure-like” pattern of edema (see [Figure 3e](#)). [Table 2](#) summarizes the grading of retinal ischemic edema. In 34 of these cases (15.3%), pronounced retinal swelling in the macular region led to radial macular folds centered on the fovea (see [Figure 3f](#)).

A cherry-red spot was present in 199 eyes (89.6%) in this cohort. Eyes without a cherry-red spot typically exhibited milder retinal ischemic edema or harbored a large cilioretinal artery supplying the macular region. The cherry-red spot

usually had an indistinct border, with a color transition zone between the spot and the surrounding whitish, edematous retina (see Figure 3c and e). However, in 32 eyes (16.1%), the cherry-red spot was well-defined and punched-out (see Figure 3b and f). The size of the cherry-red spot also varied. In 61 eyes (30.7%), the vertical diameter of the spot was $\leq 1/3$ of optic disc diameter. The size of the cherry-red spot was correlated with the final BCVA ($\chi^2 = 23.69$, $*p < 0.001$): Eyes with a spot vertical diameter $\leq 1/3$ optic disc diameter had a worse visual outcome.

Cotton-wool spots-also a manifestation of acute retinal ischemia (see Figure 3e), were observed in 119 eyes (53.6%) at presentation. These spots were predominantly distributed around the optic disc and near the superior and inferior vascular arcades. No correlation was found between the final BCVA and the presence of cotton-wool spots ($\chi^2 = 0.738$, $p = 0.390$).

Retinal hemorrhages unrelated to diabetic retinopathy were observed in 28 eyes (12.6%). These hemorrhages were exclusively distributed around the optic disc or near the retinal vascular arcades (see Figure 3g), presenting as focal, patchy, or flame-shaped lesions located in the superficial retinal layers. Retinal hemorrhages were adjacent to the distribution of the cilioretinal artery present in 14 of these 28 eyes (50%). Pearson's chi-square analysis revealed a significant correlation between the presence of retinal hemorrhages and the presence of cilioretinal artery ($\chi^2 = 5.35$, $p = 0.021$). However, no significant correlation was found between retinal hemorrhages and final BCVA ($\chi^2 = 3.062$, $p = 0.080$).

Relationship Between Fundus Changes and Time Since CRAO Onset

As shown in Table 3, a significant correlation existed between the time since symptom onset and fundoscopic findings at presentation. The grade ($\chi^2 = 15.6$, $p < 0.001$) and pattern ($\chi^2 = 39.1$, $p < 0.001$) of retinal ischemic edema, the border ($\chi^2 = 7.89$, $p = 0.019$) and size ($\chi^2 = 11.92$, $p = 0.003$) of the cherry-red spot, the presence of retinal hemorrhage ($\chi^2 = 7.16$, $p = 0.028$), cotton wool spots ($\chi^2 = 8.47$, $p = 0.014$), macular folds ($\chi^2 = 15.10$, $p = 0.001$) and retinal arterial narrowing ($\chi^2 = 6.07$, $p = 0.048$) were all significantly correlated with the time from symptom onset to presentation.

Table 3 The Correlation Between Fundus Changes and Time Since CRAO Onset

		Overall (n=222)	Time Since CRAO Onset			p value
			≤ 3 Days (n = 144)	4-7 Days (n = 48)	> 7 Days (n = 30)	
Optic disc (n, %)	Disc palor	78 (35.1)	53 (36.8)	15 (31.3)	10 (33.3)	0.765
	Margin blurring	80 (36.0)	59 (41.0)	14 (29.2)	7 (23.3)	0.100
Retinal ischemic edema (n, %)	Grade 0	11 (5.0)	3 (2.1)	2 (4.2)	6 (20.0)	<0.001
	Grade 1	23 (10.4)	13 (9.0)	2 (4.2)	8 (26.7)	
	Grade 2	80 (36.0)	45 (31.3)	23 (47.9)	12 (40.0)	
	Grade 3	108 (48.6)	83 (57.6)	21 (43.8)	4 (13.3)	
Retinal edema pattern (n, %)	Fissure-like	47 (23.3)	22 (15.6)	20 (43.5)	5 (20.8)	<0.001
	Diffused	164 (77.7)	119 (84.4)	26 (56.5)	19 (79.2)	
Cherry-red spot (n, %)	Well-defined	32 (16.1)	28 (21.2)	2 (4.4)	2 (9.1)	0.019
	$< 1/3$ disc diameter	61 (30.7)	51 (38.6)	6 (13.3)	4 (18.2)	0.003
Macular folds (n, %)		34 (15.3)	32 (22.2)	1 (2.1)	1 (3.3)	0.001
Cotton-wool spot (n, %)		119 (53.6)	67 (46.5)	33 (68.8)	19 (63.3)	0.014
Hemorrhage (n, %)		28 (12.6)	13 (9.0)	10 (20.8)	7 (23.3)	0.028
Arterial narrowing (n, %)		145 (65.3)	102 (70.8)	28 (58.3)	15 (50.0)	0.048
Vascular sheathing (n, %)		10 (4.5)	9 (6.3)	1 (2.1)	0 (0)	0.213
Flow interruption (n, %)		12 (5.4)	9 (6.3)	1 (2.1)	2 (6.7)	0.514
Intravascular emboli (n, %)		5 (2.3)	5 (3.5)	0 (0)	0 (0)	0.250
Venous narrowing (n, %)		119 (53.6)	82 (56.9)	24 (50.0)	13 (43.3)	0.338
Venous dilation (n, %)		47 (21.2)	36 (25.0)	9 (18.8)	2 (6.7)	0.074

In patients presenting within 3 days of symptom onset, macular ischemic edema was more severe and predominantly diffuse. Additionally, macular folds, retinal arterial narrowing, and well defined cherry-red spots < 1/3 disc diameter were more common. By contrast, patients who presented after 3 days exhibited less severe retinal ischemic edema, with a higher proportion of the fissure-like pattern. The prevalence of retinal arterial narrowing and macular folds was significantly reduced, while the incidence of cotton-wool spots and retinal hemorrhages increased.

The Relationship Between Fundus Changes and Visual Prognosis in CRAO

Ttally177 patients were included in the regression analysis. Of these, 79 had a final BCVA ≥20/200, and 98 had a final BCVA < 20/200. Chi-square tests revealed that the following factors were correlated with final BCVA: BCVA at presentation, grade of retinal ischemic edema, presence of macular folds, size of the cherry-red spot, clarity of the optic disc margin, presence of a cilioretinal artery supplying the macula, and retinal venous narrowing. These significant factors were incorporated into the logistic regression model. Multivariate logistic regression analysis revealed that BCVA at presentation, grade of retinal ischemic edema, clarity of the optic disc margin, diameter of the cherry-red spot, and the presence of a cilioretinal artery supplying the macula were significant factors affecting visual prognosis in CRAO. These factors can thus independently serve as predictive factors. A better initial BCVA, milder retinal ischemic edema, or the presence of a cilioretinal artery supplying the macula predicted a more favorable visual outcome. Conversely, an indistinct optic disc margin or a cherry-red spot diameter ≤ 1/3 of the optic disc diameter predicted a poor visual prognosis in CRAO. The results of the analysis are presented in Table 4.

Discussion

The retinal pathological changes constitute the most direct evidence for diagnosing CRAO and serve as a critical basis for assessing the severity of the condition. By reviewing the fundus photographs of 222 CRAO patients at admission, this study found that the main fundoscopic changes upon presentation included retinal ischemic edema, cherry-red spot, retinal arterial and/or venous narrowing, blurring of the optic disc margin, and cotton-wool spots. Other less common alterations included retinal hemorrhages, venous dilation, and macular folds. Logistic regression analysis identified

Table 4 Logistic Regression Analysis of Factors Associated with Visual Prognosis in CRAO

		Final BCVA		OR (95% CI)	OR (95% CI)*
		0:≥0.1	1:<0.1		
Baseline BCVA	≤FC	46(58.2%)	90(91.8%)		
	FC-20/200	14(17.7%)	6(6.1%)	0.219 (0.079, 0.608)	0.220 (0.077, 0.624)
	≥20/200	19(24.1%)	2(2.0%)	0.054 (0.012, 0.214)	0.067 (0.015, 0.307)
				p for trend<0.001	p for trend<0.001
Macular edema	Grade 0/1	15(19%)	4(4.1%)		
	Grade 2	33(41.8%)	31(31.6%)	3.523 (1.054, 11.778)	3.504 (1.008, 12.174)
	Grade 3	31(39.2%)	63(64.3%)	7.621 (2.333, 24.895)	8.169 (2.408, 27.709)
				p for trend<0.001	p for trend<0.001
Macular folds	No	73(77.6%)	76(92.4%)		
	Yes	6(7.6%)	22(22.4%)	3.522 (1.351, 9.181)	2.677 (1.000, 7.169)
Cherry-red spot	≤1/3 DD	9(12.9%)	40(43.0%)		
	>1/3 DD	61(87.1%)	53(57.0%)	0.195 (0.087, 0.440)	0.218 (0.094, 0.507)
Disc margin	Clear	62(78.5%)	49(50.0%)		
	Blurring	17(21.5%)	49(50.0%)	3.647 (1.872, 7.105)	4.133 (2.010, 8.496)
Cilioretinal artery of grade 3/4	No	59(74.7%)	93(94.9%)		
	Yes	20(25.3%)	5(5.1%)	0.159 (0.056, 0.446)	0.165 (0.058, 0.465)
Venous dilation	No	44(55.7%)	37(37.8%)		
	Yes	35(44.3%)	61(62.2%)	2.073 (1.134, 3.789)	1.821 (0.970, 3.417)

Note: *Adjusted the time since CRAO onset and patent cilioretinal artery (cilioretinal arteries of grade 3/4).
Abbreviations: FC, finger counting; DD, disc diameter.

BCVA at presentation, the grade of retinal ischemic edema, clarity of the optic disc margin, size of the cherry-red spot, presence of macular folds, and a cilioretinal artery supplying the macula as factors influencing the final visual outcome in CRAO. These factors can therefore serve as independent predictors for visual prognosis in CRAO.

Retinal Ischemic Edema and Cherry-Red Spot in CRAO

The most prominent funduscopic finding in CRAO is retinal ischemic edema. Acute ischemia results in retinal intracellular edema and coagulative necrosis, manifesting as grayish-white opacification upon ophthalmoscopic examination or fundus photography. The macula has the highest cellular density, and exhibits the most pronounced grayish-white opacification in CRAO, whereas the peripheral retina—with lower cellular density and thinner structure—shows minimal morphological changes.²⁰ The central foveola contains only photoreceptors and is primarily nourished by the choroid. It remains transparent in CRAO, making the underlying color of the choroid and retinal pigment epithelium visible, and presenting the “cherry-red spot”. Cherry-red spot sometimes is absent in CRAO.²¹ Hayreh reported a noticeable cherry-red spot appeared within 20 minutes after the central retinal artery was blocked in animal CRAO models.²² In this study, the severity of retinal ischemic edema was graded by comparison with standard photographs. Lower-grade edema often coexisted with a poorly defined cherry-red spot. Severe retinal ischemia can lead to significant tissue swelling, which leads to macular folds. This swelling compresses the cherry-red spot, reducing its size and sharpening its borders. Both the grade of retinal edema and the morphology of the cherry-red spot can serve as indicators for assessing CRAO severity.

In some CRAO cases, a narrow peri-artery retinal band with relatively normal color can be observed, resulting in a “fissure-like” pattern of edema. This indicates that residual blood flow within the retinal artery may support the immediate perivascular avascular zone, thereby preventing the development of ischemic edema in this area or facilitating its resolution. This study found that the presence of fissure-like edema was associated with the time since symptom onset. The proportion of eyes with fissure-like edema was only 15.6% among those presenting within 72 hours of onset. This proportion nearly doubled in patients presenting at 4–7 days. Concurrently, the proportion of eyes with diffuse edema decreased by one-third. This finding suggests the recovery of retinal blood flow during CRAO.

Disc Changes in CRAO

Disc pallor and margin blurring are the primary alterations of the optic disc in CRAO, and they may occur in isolation or coexist.

In animal models of CRAO, Hayreh observed that disc pallor could occur as early as 7 minutes after the CRAO onset.²² Among patients presenting within 1 week of CRAO onset, 27.2% exhibited optic disc pallor. In the present study, a higher proportion (35.1%) of eyes with CRAO showed optic disc pallor upon presentation. Statistical analysis revealed that disc pallor was correlated with retinal arterial narrowing, venous narrowing, and venous dilation ($\chi^2 = 19.77, 32.39, 6.686$, respectively; $p < 0.001, < 0.001, = 0.01$, respectively). Disc pallor was more common in eyes with retinal arterial/venous narrowing, while less frequently observed in eyes with retinal venous dilation. Based on these findings, we propose that disc pallor in CRAO should be attributable to optic disc circulatory disturbance, rather than edema of the superficial nerve fiber layer.²⁰

It has been reported that 16.9% of CRAO patients presenting within 1 week of symptom onset exhibited optic disc edema.²⁰ In the present study, optic disc margin blurring was observed in 36.0% of eyes with CRAO, with the superior and inferior disc poles being most prominently involved. This margin blurring often coexisted with other signs of severe retinal ischemia, such as retinal arterial narrowing and disrupted blood flow, and correlated with the grade of macular edema. Typically, CRAO does not induce optic disc swelling or elevation, unless complicated by anterior ischemic optic neuropathy (AION) or other optic nerve disorders. Instead, it presents solely as disc margin blurring, which arises from edema of the retinal nerve fiber layer (RNFL) rather than from primary optic disc pathology. Therefore, using the term “optic disc edema” to describe this sign may be misleading. We recommend the more precise description “blurring of the optic disc margin” to avoid conceptual ambiguity.

Retinal Vascular Changes in CRAO

Retinal arterial alterations are crucial diagnostic evidence for CRAO, primarily including arterial narrowing, blood flow disruption, and intravascular emboli. In the present study, complete interruption of retinal blood flow was rare; instead, residual blood flow persisted within the arteries in most cases. Arterial narrowing was observed in 65.3% of eyes at presentation—a proportion significantly higher than that reported in Hayreh's study.²⁰ This discrepancy may be explained by the timing of patient presentation: the majority of patients in our cohort were evaluated within 1 week of symptom onset. Given the time-dependent progression of fundus manifestations in CRAO, retinal arterial narrowing is more pronounced during the disease early stage. Retinal arterial emboli were identified in only 2.3% of eyes with CRAO in this series, all of which were bright, yellowish cholesterol emboli. By contrast, Hayreh reported a detection rate of emboli as high as 69%.²⁰ This substantial discrepancy may be attributed to two key factors. First, our embolus assessment relied solely on fundus photographs that likely missed emboli located in the peripheral retina. Second, Hayreh's embolus diagnosis was based on repeated evaluations conducted over multiple follow-up visits, —an approach that better captured the temporal and spatial multifocality of embolic distribution within the retinal vasculature.

Retinal vein alterations primarily include venous narrowing and venous dilation. Venous narrowing in CRAO often coexists with arterial narrowing, whereas retinal venous dilation is a frequently overlooked sign. In the present study, this sign was observed in 47 eyes (21.2%). Venous dilation was characterized not only by an increase in venous diameter but also by a reduced tapering of the venous lumen upon branching, resulting in a diminished caliber difference between the major venous trunk and its tributaries. Retinal venous dilation may indicate either partial retinal reperfusion or impaired vascular autoregulation.

Other Retinal Changes in CRAO

Retinal hemorrhage can also occur in CRAO. In this study, 28 eyes (12.6%) exhibited retinal hemorrhages. These hemorrhages were focal, patchy, or flame-shaped, exclusively, and distributed near the optic disc, around the retinal vascular arcades, or adjacent to the perfusion area of a cilioretinal artery. All these regions have relatively better blood supply. It has been proposed that these superficial flame-shaped or patchy hemorrhages are related to arterial perfusion pressure. Retinal ischemia may impair the blood-retinal barrier, which becomes susceptible to rupture under intraluminal perfusion pressure.²³ Compared to deeper capillary networks, the superficial capillaries are subjected to greater perfusion pressure, which may explain why hemorrhages in CRAO often appear flame-shaped or patchy. Retinal hemorrhages were more prevalent in CRAO cases presenting beyond 3 days of symptom onset. This finding suggests that incomplete retinal reperfusion occurring at a certain time point following retinal artery occlusion under ischemic conditions.

Predictive Factors for Visual Prognosis in CRAO

A review of the existing literature reveals that some patients with CRAO may achieve visual improvement even in the absence of treatment, whereas some others would suffer from persistent severe visual impairment, despite receiving the most aggressive interventions administered immediately after symptom onset. Previous studies on CRAO often selected participants based primarily on factors such as time since symptom onset and the presence of a cilioretinal artery, without comprehensively evaluating the overall retinal condition to predict visual prognosis. This approach may introduce selection bias and confounding factors, thereby influencing the research outcomes. Therefore, to some extent, predicting the potential for visual recovery and carefully selecting appropriate CRAO cases—before initiating clinical studies—are more critical than the choice of interventional treatment itself.

Research on visual prognosis prediction in CRAO remains relatively limited. Hayreh,² Schmidt¹¹ and Ahn²⁴ all found that CRAO classification was associated with visual prognosis. Since the classification is primarily based on findings from funduscopy and fluorescein angiography (FFA), their work indirectly supports a link between funduscopy or FFA changes and CRAO visual prognosis. Hadanny et al found that the presence of a cherry-red spot was correlated with visual prognosis of CRAO; those with a cherry-red spot had poorer vision, while conversely, the visual prognosis was better in its absence.⁶ Gong et al categorized CRAO into three types based on angiographic findings: hypoperfusion, exudative, and mixed. They demonstrated that this angiographic classification correlated with the degree of visual impairment, with the exudative type

exhibiting a more favorable visual prognosis than the hypoperfusion or mixed types.¹² Alterations on optical coherence tomography (OCT) in eyes with CRAO also correlate with visual prognosis. Specifically, the retinal thickness shows a positive correlation with logMAR visual acuity.^{13–16} Furthermore, Chen et al demonstrated that final logMAR visual acuity was mildly or moderately correlated with retinal thickness and strongly correlated with the optical intensity of photoreceptor/retinal pigment epithelium and optical intensity ratio.¹⁶ On B-scan ultrasonography, a “spot sign” posterior to the optic disc in CRAO indicates an embolus and is often associated with a poor visual prognosis.^{18,19}

Visual acuity and fundoscopic findings are the most readily available clinical data for CRAO patients at presentation. These findings not only reflect the degree of retinal ischemia, but also provide information on current retinal function and circulatory status, thereby assisting clinicians in assessing disease severity and predicting visual prognosis. Identifying predictive factors from these parameters holds significant clinical value. This study focused on pathological changes in posterior pole fundus photographs of CRAO patients. Logistic regression analysis revealed that BCVA at presentation, the grade of retinal ischemic edema, the size of the cherry-red spot, presence of a patent cilioretinal artery and the clarity of the optic disc margin were all associated with visual outcome, and could serve as independent predictive factors for visual prognosis in CRAO. A better initial BCVA, milder retinal ischemic edema, or the presence of a cilioretinal artery supplying the macula predicted a more favorable visual outcome. By contrast, an indistinct optic disc margin or a cherry-red spot with a diameter $\leq 1/3$ of the optic disc diameter indicated a poor visual prognosis.

Conclusion

Common fundoscopic changes in acute CRAO include retinal ischemic edema, cherry-red spot, retinal arterial and/or venous narrowing, blurring of the optic disc margin, and cotton-wool spots, as well as other less frequent alterations such as retinal hemorrhages, venous dilation, and macular folds. The fundus changes in acute CRAO were correlated with the visual prognosis. Visual acuity at presentation, grade of retinal ischemic edema, clarity of the optic disc margin, size of the cherry-red spot, and the presence of a cilioretinal artery supplying the macula could be predictive factors for visual prognosis in CRAO.

Data Sharing Statement

The de-identified data used to support the findings of this study are available from the corresponding author (Prof. Minglian Zhang, email: zhmyk@sohu.com; Prof. Xiaorong Li, xiaorli@163.com) on reasonable request.

Ethics

This study was conducted with approval by the Hebei eye Hospital Institutional Review Board (ethics approval number: 2024KY42), which waived the requirement for individual informed consent due to the retrospective nature of the research. All procedures adhered to the tenets of the Declaration of Helsinki. All patient data were de-identified and anonymized prior to analysis to ensure confidentiality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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