· Original article ·

Comparative study on clinical characteristics of patients with retinal artery occlusion in different age groups

Huang Chanjuan, Yuan Huhai*, Xu Haiyan, Peng Zirui, Liu Pai, Yuan Rongdi*

引用:黄婵娟,袁湖海,徐海燕,等. 不同年龄组视网膜动脉阻塞患者临床特征的对比研究. 国际眼科杂志, 2026, 26(10): 1690-1697.

Department of Ophthalmology, the Second Affiliated Hospital of Army Medical University, Chongqing 400038, China
* Co-first authors: Huang Chanjuan and Yuan Huhai
Correspondence to: Yuan Rongdi. Department of Ophthalmology, the Second Affiliated Hospital of Army Medical University, Chongqing 400038, China. yuanrongdi@tmmu.edu.cn
Received: 2025-12-02 Accepted: 2026-07-01

不同年龄组视网膜动脉阻塞患者临床特征的对比研究

黄婵娟*,袁湖海*,徐海燕,彭子芮,刘 派,袁容娣
作者单位:(400038)中国重庆市,陆军军医大学第二附属医院眼科
*黄婵娟和袁湖海对本文贡献一致。
作者简介:黄婵娟,毕业于陆军军医大学,硕士,主治医师,助教,研究方向:缺血性视网膜疾病;袁湖海,毕业于陆军军医大学,硕士,住院医师,研究方向:视网膜动脉阻塞。
通讯作者:袁容娣,毕业于陆军军医大学,博士,主任医师,教授,研究方向:糖尿病视网膜病变、视神经损伤与修复. yuanrongdi@tmmu.edu.cn

摘要

目的:比较不同年龄组视网膜动脉阻塞(RAO)患者在病因学、危险因素、性别分布及急性期临床表现方面的差异,揭示年龄相关的异质性特征。

方法:本研究采用回顾性比较队列设计,纳入 RAO 患者并根据年龄分为<50 岁组与≥50 岁组。依据改良 TOAST 标准进行病因分型,比较两组在危险因素、病因构成及性别分布上的差异;同时在急性中央视网膜动脉阻塞(CRAO)病例中进一步评估其眼底特征与视力预后。

结果:本研究共纳入 145 例 RAO 患者,分为<50 岁组(女 15 例,男 13 例,平均年龄 36.64±9.72 岁)与≥50 岁组(女 38 例,男 79 例,平均年龄 63.50±9.54 岁)。其中<50 岁组高血压(46.4% *vs* 85.5%)及糖尿病(3.6% *vs* 27.4%)的患病率均显著低于≥50 岁组(均 $P<0.001$)。病因构成方面,<50 岁组以其他确定病因(SOE)为主(35.7% *vs* 2.6%, $P<0.001$),而≥50 岁组则以小动脉闭塞(SAO,35.9%)和大动脉粥样硬化(LAA,31.6%)占主导,两者在≥50 岁组的发生率均显著高于<50 岁组(均 $P<0.001$)。<50 岁组女性比例更高(53.6% *vs* 32.5%, $P=0.039$)。多变量分析显示,LAA 与高龄独立相关,而 SOE 与年轻独立相关。Boxcarring 征仅见于≥50 岁组患者[39.5%(17/43) *vs* 0, $P=0.011$]。

结论:<50 岁组 RAO 患者以非动脉粥样硬化性病因为主,且女性占比更高;而≥50 岁组患者则主要由动脉粥样硬化相关病因驱动,并表现出血管代偿能力减退的征象。上述发现提示,在制定 RAO 的病因评估策略及管理方案时,应充分考虑年龄相关的差异。

关键词:视网膜动脉阻塞;危险因素;病因;高血压;动脉粥样硬化

Abstract

• AIM: To examine differences in etiology, risk factors, gender, and acute-phase manifestations of retinal artery occlusion (RAO) patients in different age groups, highlighting age-related heterogeneity.

• METHODS: This retrospective comparative cohort study enrolled patients with RAO. Patients were divided into <50 y group and ≥50 y group. Etiological classification was based on modified TOAST criteria. Comparisons assessed the prevalence of risk factors, etiological distribution, sex ratio, and, in cases of acute central retinal artery occlusion (CRAO), fundus characteristics and visual outcomes.

• RESULTS: This study included a total of 145 RAO patients, which were divided into two groups based on age: <50 y group (15 females and 13 males) with the mean age of 36.64±9.72 y, and ≥50 y group (38 females and 79 males) with the mean age of 63.50±9.54 y. Hypertension (46.4% *vs* 85.5%) and diabetes (3.6% *vs* 27.4%) were less prevalent in <50 y group (both $P<0.001$). The <50 y group was characterized predominantly by stroke of other determined etiology (SOE, 35.7% *vs* 2.6%, $P<0.001$), whereas the ≥50 y group was dominated by small artery occlusion (SAO, 35.9%) and large artery atherosclerosis (LAA, 31.6%), the incidence rates were significantly higher in the ≥50 y group than in the <50 y group (both $P<0.001$). Females were more frequently represented in <50 y group (53.6% *vs* 32.5%, $P=0.039$). Multivariable analysis demonstrated that LAA was independently linked to older age and SOE to younger age. Boxcarring occurred exclusively in ≥50 y patients [39.5% (17/43) *vs* 0, $P=0.011$].

• CONCLUSION: The RAO patients <50 y predominantly present with non-atherosclerotic causes and a higher proportion of females, whereas patients ≥50 y are mainly affected by atherosclerosis driven etiologies and show signs of reduced vascular compensatory capacity. These findings indicate that age-related differences in RAO

should be taken into account when determining etiologic evaluation and management strategies.

• KEYWORDS: retinal artery occlusion; risk factors; etiology; hypertension; atherosclerosis
DOI:10.3980/j.issn.1672-5123.2026.10.03

Citation: Huang CJ, Yuan HH, Xu HY, et al. Comparative study on clinical characteristics of patients with retinal artery occlusion in different age groups. Guoji Yanke Zazhi (Int Eye Sci), 2026, 26(10):1690-1697.

INTRODUCTION

Retinal artery occlusion (RAO) is a category of retinal vascular diseases that may cause severe visual impairment, occurring mainly in the elderly population[1]. Approximately 10% of cases involve younger patients[2]; in this subgroup, the etiologic spectrum is broader and includes a higher proportion of nontraditional causes such as cardioembolism (CE), inherited or acquired hypercoagulable states, and vasculitis[3]. Accurate identification of the etiology is critically important for treatment decisions and prognostic evaluation; however, for a long time, etiological diagnosis of RAO has lacked a unified standardized system, leading to inconsistent classifications and limited comparability of research data. In recent years, the ischemic stroke etiological classification Trial of Org 10172 in Acute Stroke Treatment (TOAST) has been introduced into RAO-related studies[4], providing a reference tool for systematic etiological assessment. RAO closely resembles ischemic stroke in its pathophysiological mechanisms, and both conditions share similar risk factors and etiological profiles[5-6]. Therefore, applying the TOAST framework for etiological classification of RAO is appropriate. Currently, few studies have systematically compared RAO patients in different age groups using a standardized classification system. This study aims to apply TOAST classification to compare differences in etiologic composition, risk factors, and clinical characteristics between RAO patients aged <50 y and those aged ≥50 y, to clarify the age-related heterogeneity of RAO and provide a reference for individualized diagnosis and treatment.

PARTICIPANTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Board of the hospital under study number 2024-LYD 405-01 and adhered to the principles of the Declaration of Helsinki. Informed consent was waived because of the retrospective and anonymous nature of this study.

Participants This retrospective comparative cohort study included all patients diagnosed with RAO at the Second Affiliated Hospital of Army Medical University between January 1, 2022, and September 30, 2024. Patients were divided into two groups based on age: <50 y group (n=28) and ≥50 y group (n=117), allowing for comparison of etiological characteristics, clinical features, and outcomes between age groups.

Auxiliary Examination Patients underwent a comprehensive medical and ophthalmic history and examination. Investigations were conducted based on associated history and clinical findings. These included hemogram with vasculitis screening profile (anti ds-DNA antibody, ANA, c-ANCA, p-ANCA), homocysteine levels, antiphospholipid antibody, anticardiolipin antibody, coagulation profile (prothrombin time, activated partial thromboplastin time, bleeding time, clotting time, protein C and S levels), syphilis serology, human immunodeficiency virus (HIV), electrocardiogram, and computed tomography (CT)/magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) brain scans as needed.

Risk Factors Conventional vascular risk factors included hypertension and diabetes mellitus. The definitions of risk factors in this study were as follows: hypertension (systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg in the chronic stage or pre-stroke treatment with anti-hypertensive medication), diabetes mellitus (fasting blood glucose concentration of 7.0 mmol/L, casual blood glucose concentration of 11.1 mmol/L, positive 75 g oral glucose tolerance test result, or glycated hemoglobin A1c concentration of 6.5% on 2 different days during hospitalization or in the chronic stage, or pre-RAO treatment with antidiabetic medication).

Etiological Analysis Currently, RAO is widely recognized as a type of stroke[6]. Therefore, this study classified RAO according to the TOAST etiological classification for acute stroke. The TOAST etiological classification includes[7]: large artery atherosclerosis (LAA), small artery occlusion (SAO), CE, stroke of other determined etiology (SOE), and stroke of undetermined etiology (SUE). According to TOAST criteria, CE is defined as an embolic event originating from the heart, which can be divided into high-risk sources and medium-risk sources. Among them, artificial heart valves (including bioprosthetic and mechanical valves) are classified as high-risk CE. The diagnosis of LAA is based on finding vascular occlusive lesions (such as vascular stenosis degree >50%, ulcer formation, or complete vascular occlusion). The diagnosis of SAO is based on cranial MRI showing lacunar infarction and the absence of clinical manifestations involving other nervous system impairments.

When the RAO subtype does not meet the criteria for CE, LAA, or SAO, and another confirmed underlying cause is identified, it is classified as SOE. SOE encompasses a range of specific causes, which can be categorized into three groups based on their origin[8]: vascular diseases (vasculitis, multiple arterial thrombosis, and other vascular causes), hematological diseases (protein S deficiency, polycythemia, and leukemia), and other rare causes (including iatrogenic, glaucoma, and pregnancy). Among these, iatrogenic causes are defined as those occurring after vitrectomy or cosmetic surgery.

TOAST classification was adjudicated by a single senior neurologist with expertise in cerebrovascular diseases, based on comprehensive review of all available clinical, imaging,

and laboratory data.

Exploratory Subgroup: Isolated RAO with Vascular Risk Factors To explore the potential burden of small vessel pathology in RAO patients, we defined an exploratory subgroup—isolated RAO with vascular risk factors (iRAOVRF)—based on the following criteria: 1) confirmed central or branch RAO by fundoscopy; 2) absence of neurological symptoms; 3) presence of hypertension or diabetes mellitus; 4) exclusion of ipsilateral large artery stenosis ≥50% (by carotid ultrasound/computed tomography angiography) and high/mediumrisk cardioembolic sources (by electrocardiography and echocardiography); 5) no evidence of other determined etiologies (*e.g.*, vasculitis, dissection, hypercoagulable states); 6) either no MRI evidence of lacunar infarction or MRI not performed.

The rationale for this subgroup stems from the anatomical and pathological continuity between the retinal central artery and cerebral perforating arteries—both originate from the internal carotid system and share similar responses to vascular risk factors[9-10]. This exploratory subgroup does not alter the primary TOAST based classification: in the main analysis, all iRAOVRF patients remain categorized as SUE per strict TOAST criteria[7]. The iRAOVRF subgroup is presented separately in secondary analyses to capture the full spectrum of potential small vessel pathology and to generate hypotheses for future prospective studies.

Clinical Characteristics and Visual Prognosis of CRAO with Onset Time Less Than 7 d This study retrospectively analyzed patients with acute central retinal artery occlusion (CRAO) with onset time ≤7 d and systematically compared the fundus photographic features, visual prognosis, and retrobulbar vascular ultrasound blood flow parameters of the healthy eye between patients under 50 years old and those 50 years old or older. Eligible patients were selected based on inclusion criteria, which required diagnosis of acute CRAO with onset time ≤7 d confirmed by fundus color photography, and exclusion criteria (combined with other retinal vascular diseases, severe refractive media opacity, previous ocular surgery history). The core observation index was boxcarring (segmental blood flow), defined as the "carriage-like" blood flow stagnation phenomenon within the retinal vessels[11].

This study retrospectively analyzed the retrobulbar hemodynamics in acute CRAO with onset time ≤7 d. Using the American GE Logiq7 color Doppler ultrasound diagnostic device, with a probe frequency of 7.5 MHz, a sample volume of 1 mm, and an angle between the ultrasound beam and blood flow direction less than 30°, the peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI) of the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary arteries were measured, respectively. Sampling of OA was located 15-20 mm behind the globe, CRA 3-5 mm posterior to the optic disc, and the short posterior ciliary arteries were measured at the nasal/temporal side of the posterior pole. Continuous recordings were made for 4-6 fluctuation cycles, and clear images were selected for measurement and calculation. The detected data were processed by computer and displayed in printed spectral images.

Statistical Analysis Descriptive statistics were reported as mean ± standard deviation for continuous variables and as percentages for categorical variables. Background characteristics were compared between adults<50 y and adults ≥50 y by Mann-Whitney *U* test, Pearson's Chi-squared test, or Fisher's exact test as appropriate. The frequencies of embolic sources or uncommon causes between adults <50 y and adults ≥50 y were tested by Fisher's exact test. Age-dependent changes in ocular blood flow indices [OA-RI and posterior ciliary artery (PCA)-RI] were assessed using Spearman's rank correlation.

Because certain subgroups had few events, Firth's penalized likelihood logistic regression was used to produce stable estimates. The models were adjusted for hypertension, diabetes, hyperglycemia, and male sex. Age was retained as a categorical variable (<50 y *vs* ≥50 y) to be consistent with the primary study design. Odds ratios (ORs) with 95%*CI* and two-sided *P* values were reported.

All analyses were performed using IBM SPSS software (version 22.0, Chicago, IL, United States). All tests were two-sided, and a *P* value of < 0.05 was considered statistically significant.

RESULTS

General Comparison This study included a total of 145 patients with acute RAO, and divided into two groups: those under 50 years old were classified as <50 y group ($n=28$), and those 50 years old or older were classified as the ≥50 y group ($n=117$). The average age of the <50 y group was 36.64±9.72 y (range 14-47 y), with females accounting for 53.6% (15/28); the average age of the ≥50 y group was 63.50±9.54 y (range 50-89 y), with a significantly lower proportion of females (32.5%, 38/117; $P=0.039$). Regarding traditional cardiovascular risk factors, the prevalence of diabetes in the <50 y group (3.6%, 1/28) was significantly lower than that in the ≥50 y group (27.4%, 32/117; $P=0.005$), and the prevalence of hypertension (46.4%, 13/28) was also significantly lower than that in the ≥50 y group (85.5%, 100/117; $P=0.000$) and intraocular pressure at presentation (≤50 y group 12.75±5.72 mmHg *vs* >50 y group 12.54±4.47 mmHg, $P=0.857$). Carotid imaging was performed in 75.0% of patients <50 y and 90.6% of patients ≥50 y ($P=0.332$). MRI noncompletion rates were 42.8% and 34.2%, respectively ($P=0.39$; Table 1).

Thrombophilia screening was not performed in 17.9% of patients<50 y and 12.8% of patients ≥50 y ($P=0.358$). Among patients without screening, the majority had alternative confirmed etiologies (LAA, CE, SOE) that determined their TOAST classification independently. Only 1.4% of the cohort ($n=2$) lacked both screening and an alternative etiology; these were classified as SUE in the primary analysis.

Analysis of Causes Etiological analysis based on the modified TOAST classification showed a significant difference in the distribution of causes between the < 5 0 y group

Table 1 Baseline characteristics

Parameters	<50 y group (n=28)	≥50 y group (n=117)	[a]P
Age (y, $\bar{x}\pm s$, range)	36.64±9.72 (14-47)	63.50±9.54 (50-89)	
Sex, n (%)			0.039
Female	15(53.6)[a]	38(32.5)	
Male	13(46.4)	79(67.5)	
Laterality, n (%)			0.866
Right	17(60.7)	69(59.0)	
Left	11(39.3)	48(41.0)	
IOP at presentation($\bar{x}\pm s$, mmHg)	12.75±5.72	12.54±4.47	0.857
Vascular risk factors, n (%)			
Diabetes	1(3.6)[a]	32(27.4)	0.005
Hypertension	13(46.4)[a]	100(85.5)	0.000
Imaging modality, n (%)			
MRI not performed	12(42.8)	40(34.2)	0.39
Carotid imaging performed	21(75)	106(90.6)	0.332
Thrombophilia screening not performed	5(17.9)	15(12.8)	0.358

IOP: Intraocular pressure; MRI: Magnetic resonance imaging. [a]P<0.05 indicates a statistically significant difference between groups.

(n=28) and the ≥50 y group (n=117). The proportion of SOE in the <50 y group was significantly higher than that in the ≥50 y group [35.7% (10/28) *vs* 2.6% (3/117); P<0.001), while LAA was significantly more common in the ≥50 y group [31.6% (37/117) *vs* 3.6% (1/28); P=0.001]. SAO was also more common in the ≥50 y group [35.9% (42/117) *vs* 14.3% (4/28); P=0.033). There was no statistically significant difference in CE (high risk+medium risk) between the two groups [<50 y group 10.7% (3/28) *vs* ≥50 y group 3.4% (4/117); P=0.131), and the difference in cryptogenic etiology between groups was also not statistically significant [<50 y group 35.7% (10/28) *vs* ≥50 y group 26.5% (31/117); P=0.330; Table 2].

Among the 14-39 age group, no cases of SAO were identified in this cohort (0/12). The proportion increased to 25% (4/16) in the 40-49 age group, 29.8% (14/47) in the 50-59 age group, 38.5% (15/39) in the 60-69 age group, and 41.9% (13/31) in patients aged 70 y and older. In patients aged 50 y and above, both hypertension (85.1%-90.3%) and SAO (29.2%-41.9%) were common, reflecting the typical age-related burden of vascular risk factors and small vessel disease in this population (Figure 1).

The exploratory iRAOVRF subgroup showed similar prevalence between age groups (21.4% *vs* 22.2%; P=0.927). When analyzed together as a small vessel pathology spectrum (SAO + iRAOVRF), the combined proportion remained significantly different between groups (35.7% *vs* 58.1%; P=0.037)

Multivariable Analysis To assess whether the observed agerelated etiologic differences were independent of traditional vascular risk factors, we performed Firth logistic regression adjusting for hypertension, diabetes, hyperlipidemia, and male sex. Key findings are summarized below.

After multivariable adjustment, LAA and SOE remained

Table 2 Etiological subtypes of RAO in <50 y versus ≥50 y patients n (%)

Etiology	<50 y group (n=28)	≥50 y group (n=117)	P
Cardioembolism	3(10.7)	4(3.4)	0.131
High-risk sources	2(7.1)	2(1.7)	
Medium-risk sources	1(3.6)	2(1.7)	
Large-artery atherosclerosis	1(3.6)	37(31.6)	0.001
Small artery occlusion	4(14.3)	42(35.9)	0.033
Other determined etiologies	10(35.7)	3(2.6)	<0.001
Cryptogenic etiology	10(35.7)	31(26.5)	0.330

RAO: Retinal artery occlusion.

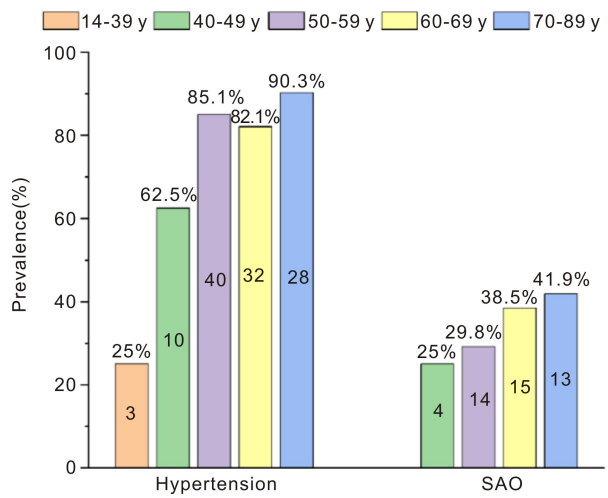

Figure 1 Hypertension prevalence and SAO incidence across age strata SAO: Small artery occlusion.

associated with age group: ≥50 y was associated with lower LAA risk (OR=0.127, P=0.005), while <50 y was associated with SOE (OR=15.15, P<0.001). In contrast, the age effect on SAO was attenuated and no longer significant after adjustment (OR=0.608, P=0.399), whereas

hypertension was associated with SAO (OR = 11.953, P < 0.001), suggesting that the age-related difference in SAO may be largely explained by the higher prevalence of hypertension in older patients. Hypertension showed a negative association with SOE (OR = 0.15, P = 0.010), while diabetes, hyperglycemia, and male sex were not significantly associated with any outcome. This negative association may reflect that hypertensive patients are more likely to be classified into other etiologic categories (*e.g.*, SAO, LAA) rather than SOE. Given the limited number of events, such as only one LAA case in the <50 y group and a total of 13 SOE events, some estimates lacked precision, as reflected by wide confidence intervals. These findings should therefore be interpreted with caution and warrant validation in larger prospective cohorts.

Analysis of Rare Causes Among the 35.7% (10/28) SOE cases diagnosed in the <50 y group, the causes showed high heterogeneity. Iatrogenic factors accounted for the highest proportion (2/10), including 2 cases of perioperative complications; followed by pregnancy-related diseases (1/10), manifested as pregnancy-induced hypertension complicated with RAO. Vascular diseases accounted for 3 cases (2 cases of vasculitis, 1 case of multiple arterial thrombosis), and hematologic diseases also accounted for 3 cases (1 case each of protein S deficiency, polycythemia vera, and leukemia). Notably, 1 case of ischemia secondary to glaucoma was also included in this category (Table 3).

Distribution of Diagnostic Types in the Two Groups CRAO was the main subtype in both groups, accounting for 64.3% (18/28) in the <50 y group and 82.9% (97/117) in the ≥50 y group. Branch retinal artery occlusion (BRAO) had a higher incidence in the <50 y group [21.4% (6/28) *vs* 10.3% (12/117) in the ≥50 y group], while the proportion of CRAO combined with central retinal vein occlusion (CRVO) was 14.3% (4/28) and 6.8% (8/117), respectively. According to the Chi-square test, the overall difference in subtype distribution among the three groups was not statistically significant (P = 0.218), as detailed in Table 4.

Fundus Features and Visual Prognosis in Acute CRAO In this cohort of acute CRAO patients with onset within 7 d (13 *vs* 43 eyes), we evaluated the age-related differences in fundus findings. This study found that boxcarring has a significant age-dependent characteristic: it is only seen in the ≥50 y group [39.5% (17/43)] and completely absent in the <50 y group (0/10; P=0.011), suggesting that this sign may be related to age-associated vascular sclerosis or chronic ischemia. Cherry red spots (<50 y group 70.0% *vs* ≥50 y group 83.7%, P = 0.318), optic disc edema (70.0% *vs* 58.1%, P=0.490), cotton wool spots (10.0% *vs* 30.2%, P=0.258), and retinal hemorrhage (40.0% *vs* 23.3%, P=0.279) showed no intergroup differences, indicating that these acute retinal ischemic signs are core clinical manifestations of CRAO and are unrelated to age (Table 5).

Table 3 Frequency of uncommon causes in <50 y group *n* (%)

SOE subtype	<50 y group(n=28)
Other vascular cause	3(10.7)
Vasculitis	2(7.1)
Multiple arterial emboli	1(3.6)
Hematologic disease	3(10.8)
Protein S deficiency	1(3.6)
Polycythemia	1(3.6)
Leukaemia	1(3.6)
Other disease	4(14.3)
Iatrogenic	2(7.1)
Glaucoma	1(3.6)
Pregnancy	1(3.6)

SOE: Stroke of other determined etiology.

Table 4 Distribution of RAO subtypes in groups *n* (%)

Type	<50 y group (n=28)	≥50 y group (n=117)	P
CRAO	18(64.3)	97(82.9)	
BRAO	6(21.4)	12(10.3)	
CRAO with CRVO	4(14.3)	8(6.8)	0.218

RAO: Retinal artery occlusion; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion.

The analysis of visual prognosis showed no statistically significant difference in initial visual acuity (LogMAR 2.0±1.1 *vs* 2.2±0.8, P=0.326) and final visual acuity (1.7±1.0 *vs* 1.9±0.9, P=0.441) between groups (Table 5).

Age-Related Hemodynamic Changes in the Healthy Eye of Acute CRAO We analyzed the retrobulbar hemodynamic parameters in the healthy eye of 55 patients with acute CRAO (onset ≤7 d) to assess their correlation with age. RI of OA significantly increases with age (r=0.38, P=0.023); the RI of the posterior ciliary artery also shows a positive correlation with age (r = 0.32, P = 0.046). Notably, the blood flow parameters (PSV, EDV, and RI) of CRA are not significantly associated with age (all P>0.05; Figure 2).

Characteristics of Patients Under 40 y Descriptive analysis of the 12 patients under 40 y of age revealed a diverse etiological spectrum. SOE accounted for 50.0% (n=6), with causes including protein S deficiency, post-vitrectomy status,

leukemia-associated hyperviscosity, herpes virus-related optic perineuritis, early pregnancy, and glaucoma. No cases of definite cerebral SAO were observed among the 8 patients who completed MRI. Due to the small sample size, no statistical comparisons were performed.

DISCUSSION

Atherosclerotic risk factors are well established as major contributors to RAO. In our young RAO cohort, the prevalence of hypertension (46.4%) and diabetes (3.6%) aligned closely with previously reported data (41.4% and 5.6%, respectively)[12], supporting the representativeness of our study population. More importantly, significant age-related differences emerged: hypertension (46.4% *vs* 85.5%) and diabetes (3.6% *vs* 27.4%) were markedly less common in the <50 y group than in the ≥50 y group (both $P<0.05$). This divergence in risk factor burden was directly mirrored in the etiologic spectrum. The <50 y group was characterized predominantly by SOE (35.7%) and SAO (14.3%). In contrast, the ≥50 y group exhibited a clear atherosclerosis dominant pattern, with LAA (29.1%) and SAO (35.9%) together accounting for the majority of cases. These findings suggest that the higher prevalence of traditional cardiovascular risk factors in older RAO patients is closely associated with the predominance of atherosclerotic etiologies in this age group.

In RAO patients <50 y, SAO was observed only in those aged 40-49 y (18.8%), consistent with a previous study reporting higher SAO risk in patients aged 45-50 y compared with those under 45 y in cerebral infarction[13]. However, multivariable analysis revealed that this agerelated pattern was largely explained by hypertension: after adjusting for hypertension, the association between age and SAO was no longer significant ($OR=0.608$, $P=0.399$), whereas hypertension remained a strong independent predictor ($OR=11.953$, $P<0.001$). These findings suggest that the increased risk of SAO during middle age is driven primarily by the accumulation of hypertension rather than age itself. Therefore, hypertension, a modifiable risk factor, deserves particular attention in the prevention and management of SAO in RAO patients.

In patients with RAO, the proportion of those with SOE is significantly higher in the <50 y group than in the ≥50 y group. This significant difference strongly suggests that the spectrum of causes in RAO patients <50 y is fundamentally different from that in patients ≥50 y, highlighting the important clinical value of conducting more in-depth and systematic etiological studies in the younger population. In the subgroup analysis of SOE in the younger group, vasculitis is the primary cause, accounting for 30%, which is highly consistent with the previously reported 28% in the literature[8]. Additionally, we observed causes such as polycythemia[14], leukemia[15], and protein S deficiency syndrome[16] among the SOE patients <50 y. These findings collectively indicate that compared to patients ≥50 y whose RAO is mainly attributed to atherosclerotic thrombosis, the pathogenesis in RAO patients <50 y, especially those lacking traditional vascular risk factors, requires more attention to non-atherosclerotic pathways, including embolic diseases, hypercoagulable states, or inflammatory diseases.

Table 5 Age-based differences in clinical signs and visual outcomes of acute CRAO

Parameters	<50 y group ($n=10$)	≥50 y group ($n=43$)	P
Cherry red spot, n (%)	7(70.0)	36(83.7)	0.318
Boxcarring, n (%)	0	17(39.5)	0.011
Optic disk edema, n (%)	7(70.0)	25(58.1)	0.490
Retinal hemorrhage, n (%)	4(40.0)	10(23.3)	0.279
Cotton wool spots, n (%)	1(10)	13(30.2)	0.258
Initial visit vision ($\bar{x}\pm s$, LogMAR)	2.0±1.1	2.2±0.8	0.326
Visual prognosis ($\bar{x}\pm s$, LogMAR)	1.7±1.0	1.9±0.9	0.441

CRVO: Central retinal vein occlusion.

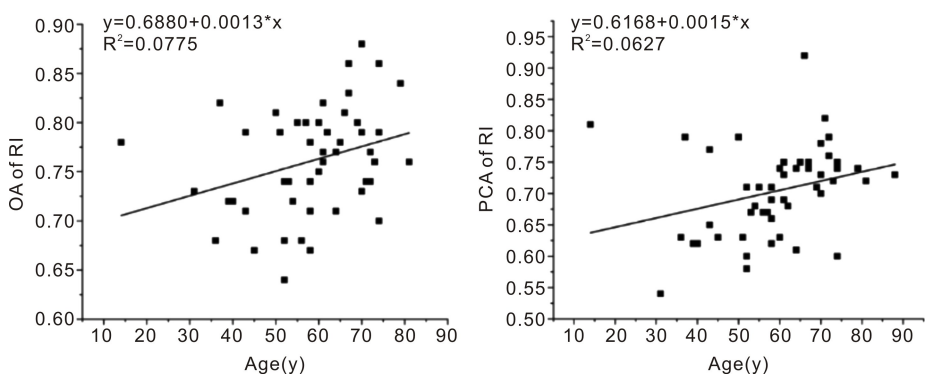

Figure 2 Correlation between RI of OA and PCA and age A: OA-RI shows a significant positive correlation with age (linear regression equation: $y=0.00013x+0.6880$; $R^2=0.0775$, $P=0.023$); B: PCA-RI shows a positive correlation trend with age (linear regression equation: $y=0.0015x+0.6168$; $R^2=0.0627$, $P=0.046$). OA: Ophthalmic artery; PCA: Posterior ciliary artery. RI: Resistive index.

This study found that the proportion of females in the RAO patients <50 y was significantly higher than that of males. This gender distribution characteristic contrasts sharply with the male-dominated pattern commonly observed in large RAO registry studies[17]. The possible mechanism behind this difference involves hormonal factors. Pregnancy has been definitively confirmed to significantly increase the risk of thromboembolism in women of childbearing age[18], and its underlying pathophysiological basis may lie in the synergistic effect of progesterone-induced hypercoagulable state and endothelial dysfunction associated with estrogen fluctuations, jointly promoting thrombosis. Given the inherent thromboembolic susceptibility of women of childbearing age, patent foramen ovale (PFO) as a potential source of embolism theoretically may contribute more to the onset of RAO in young women than in men[19-20]. Furthermore, several RAO-related specific etiologies, such as autoimmune diseases (*e.g.*, Sjögren's syndrome[21]) and cardiac myxoma[22], are themselves predominantly distributed in the female population. Therefore, for women of childbearing age with RAO who lack traditional vascular risk factors (such as hypertension, diabetes, heavy smoking), systematic targeted evaluation is strongly recommended. This should include: 1) comprehensive coagulation function screening (with emphasis on antiphospholipid antibodies, protein C/S activity, *etc.*); 2) exclusion of cardiogenic embolic sources (transesophageal echocardiography is recommended); and 3) testing of relevant immunological markers.

Boxcarring (segmental blood flow) is a characteristic fundus sign in the acute phase of CRAO, reflecting severe retinal edema and intraretinal blood flow stasis, and is closely associated with poor visual prognosis[11,23-24]. This study found that the incidence of boxcarring in CRAO patients ≥50 y was significantly higher than that in the <50 y group. Further research revealed the underlying vascular physiological mechanism: in the unaffected eye of acute CRAO patients, RI of OA and PCA were both significantly positively correlated with age. This elevated RI indicates increased perfusion resistance in the distal vascular bed, whose pathophysiological basis may be related to age-associated decline in arterial wall compliance and increased arteriosclerosis. Therefore, the appearance of boxcarring not only marks severe retinal ischemia/edema but its significant age-dependent distribution more profoundly reflects the pathological process of systemic arterial elasticity deterioration with aging. The higher incidence of boxcarring in patients ≥50 y directly manifests their reduced compliance of the ophthalmic arterial system and increased blood flow resistance, making severe blood flow stasis and retinal microcirculation collapse more likely to occur in the acute CRAO state.

Based on the significant differences revealed by this study in the etiological spectrum and risk factor burden among age groups, we propose an age-stratified diagnostic and treatment strategy for patients with RAO: for RAO patients under 50 years old, it is recommended to prioritize systematic screening for SOE causes, especially for those lacking traditional risk factors such as hypertension and diabetes. The screening should focus on: 1) evaluation of hypercoagulable states (antiphospholipid antibody profile, protein C/S/antithrombin III activity, coagulation factor gene mutations, *etc.*); 2) embolic source investigation (transesophageal echocardiography to detect cardiogenic sources or patent foramen ovale, carotid ultrasound, *etc.*); 3) detection of inflammation/vasculitis indicators (such as ANCA, inflammatory markers, vascular imaging).

For RAO patients over the age of 50: since atherosclerotic causes (SAO+LAA) dominate absolutely in this group and traditional cardiovascular risk factors (hypertension 85.5%, diabetes 27.4%) are highly prevalent, the focus of diagnosis and treatment should shift to a comprehensive systemic atherosclerosis assessment and management. This includes: 1) strict control of cardiovascular risk factors (blood pressure lowering, glucose lowering, lipid regulation, smoking cessation); 2) assessment of systemic atherosclerotic burden (carotid/intracranial artery imaging, coronary artery risk evaluation); 3) initiation or optimization of guideline-based secondary preventive antithrombotic therapy (such as antiplatelet or anticoagulant treatment).

This study has several limitations. First, the single-center retrospective design resulted in a relatively small sample size of RAO patients <50 y, limiting statistical power for certain rare etiologic subtypes and precluding meaningful subgroup analysis of patients under 40 y. Second, some diagnostic data (*e.g.*, specific vascular imaging, complete laboratory tests) were missing from electronic medical records, which may affect the accuracy of etiologic classification. Third, the study did not include genetic susceptibility markers, oxidative stress indicators, or detailed lifestyle factors (*e. g.*, abdominal obesity, exercise, alcohol consumption, dietary structure) that may play important roles in RAO pathogenesis, particularly in patients <50 y.

Future research should focus on: 1) multicenter prospective cohort studies with larger samples to validate our findings, particularly regarding the etiological characteristics of RAO in patients under 40 y and the unique profile observed in young women, as well as the effectiveness of stratified treatment strategies; 2) deeper exploration of molecular mechanisms underlying early-onset and specific etiologic types, including genetics, epigenetics, inflammatory pathways, and thrombotic tendencies; 3) assessment of lifestyle factors and novel biomarkers in predicting RAO risk and guiding individualized intervention under more comprehensive data collection systems.

Conflicts of Interest: Huang CJ, None; Yuan HH, None; Xu HY, None; Peng ZR, None; Liu P, None; Yuan RD, None.

Authors' Contributions: concept and design (Huang CJ and Yuan HH), date collection (Xu HY, Peng ZR, and Liu P), critical revision of the article for important intellectual content (Yuan RD), study supervision. All the authors approved the final article.

REFERENCES

[1] Madike R, Cugati S, Chen CL. A review of the management of central retinal artery occlusion. Taiwan J Ophthalmol, 2022, 12(3): 273-281.
[2] Park SH, Kim BJ, Kim JH, et al. Incidence rates of retinal vascular occlusive diseases from 2011 to 2020 in South Korea: a nationwide cohort study. BMC Ophthalmol, 2024, 24(1): 128.
[3] Maiz AM, Murali S, Miller JML. Retinal artery occlusion in young patients without typical cardiovascular risk factors: etiologies, prognosis, and suggested work-up. Graefes Arch Clin Exp Ophthalmol, 2024, 262(11): 3577-3587.
[4] Lee J, Kim SW, Lee SC, et al. Co-occurrence of acute retinal artery occlusion and acute ischemic stroke: diffusion-weighted magnetic resonance imaging study. Am J Ophthalmol, 2014, 157(6): 1231-1238.
[5] Kim YD, Kim JY, Park YJ, et al. Cerebral magnetic resonance imaging of coincidental infarction and small vessel disease in retinal artery occlusion. Sci Rep, 2021, 11(1): 864.
[6] Jayasinghe M, Prathiraja O, Kayani AMA, et al. Central retinal artery occlusion: can we effectively manage this ocular emergency in a hospital setting? Cureus, 2022, 14(8): e27840.
[7] Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke, 1993, 24(1): 35-41.
[8] Ohya Y, Matsuo R, Sato N, et al. Causes of ischemic stroke in young adults versus non-young adults: amulticenter hospital-based observational study. PLoS One, 2022, 17(7): e0268481.
[9] Risimić D, Nikolić D, Simeunović D, et al. Correlation of atherogenic risk factors with retinal artery occlusion in adults. Med Glas (Zenica), 2014, 11(1): 110-114.
[10] Daxer B, Radner W, Fischer F, et al. Aetiology, diagnosis and treatment of arterial occlusions of the retina-a narrative review. Medicina (Kaunas), 2024, 60(4): 526.
[11] Hayreh SS, Zimmerman MB. Fundus changes in central retinal artery occlusion. Retina, 2007, 27(3): 276-289.
[12] Uppuluri A, Xia T, Zarbin MA, et al. Risk factors for central retinal artery occlusion in young patients. Can J Ophthalmol, 2021, 56(4): 270-272.
[13] Ojha R, Huang DY, An HD, et al. Distribution of ischemic infarction and stenosis of intra- and extracranial arteries in young Chinese patients with ischemic stroke. BMC Cardiovasc Disord, 2015, 15: 158.
[14] Rana V, Kumar P, Bandopadhyay S, et al. Central retinal artery occlusion in young adults at high altitude: thin air, high stakes. High Alt Med Biol, 2024, 25(2): 136-139.
[15] Zgolli H, Mabrouk S, Abdaoui M, et al. Unusual case of combined central retinal artery and vein occlusion in a patient with acute lymphoblastic leukemia. J Fr Ophtalmol, 2022, 45(4): e195-e197.
[16] Greven CM, Weaver RG, Owen J, et al. Protein S deficiency and bilateral branch retinal artery occlusion. Ophthalmology, 1991, 98(1): 33-34.
[17] Li Y, Hall NE, Pershing S, et al. Age, gender, and laterality of retinal vascular occlusion: a retrospective study from the IRIS® registry. Ophthalmol Retina, 2022, 6(2): 161-171.
[18] Zachariah KA, Yuan S, DeSancho MT, et al. Role of antiplatelets and anticoagulation therapies in pregnancy. J Clin Med, 2024, 13(24): 7757.
[19] Poisson SN, Leppert MH, Orjuela KD. Cryptogenic stroke and PFO closure: does sex matter? J Am Heart Assoc, 2023, 12(19): e031857.
[20] Chen L, Deng WJ, Palacios I, et al. Patent foramen ovale (PFO), stroke and pregnancy. J Investig Med, 2016, 64(5): 992-1000.
[21] Yang Y, Huang XX, Huo RX, et al. Sexual health in women with Sjogren's syndrome: a review. Eur J Obstet Gynecol Reprod Biol, 2023, 291: 1-9.
[22] Gaisendrees C, Gerfer S, Schlachtenberger G, et al. Cardiac tumors-sex-related characteristics and outcomes after surgical resection. J Surg Oncol, 2022, 126(4): 823-829.
[23] Hayreh SS, Zimmerman MB. Central retinal artery occlusion: visual outcome. Am J Ophthalmol, 2005, 140(3): 376-391.
[24] Egan RA, Lutsep HL. Prevalence of retinal emboli and acute retinal artery occlusion in acute ischemic stroke. J Stroke Cerebrovasc Dis, 2020, 29(2): 104446.