Association of subclinical atherosclerosis with retinal vein occlusion: A prospective, case-control study

Minhyung Lyu
Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Yonggu Lee
Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Byung Sik Kim
Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Hyun-Jin Kim
Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Rimkyung Hong
Department of Ophthalmology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Yong Un Shin
Department of Ophthalmology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Heeyoon Cho
Department of Ophthalmology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

Jeong-Hun Shin (cardio.hyapex@gmail.com)
Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea

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Abstract

Retinal vein occlusion (RVO) is known to be associated with atherosclerotic cardiovascular risk factors, but the association between specific markers of subclinical atherosclerosis has not been established. To investigate this association, we compared the results of cardiovascular examinations of 76 patients with RVO and 175 age- and sex-matched control subjects. Low-density lipoprotein cholesterol (LDL-C) level and brachial-ankle pulse wave velocity (baPWV) were significantly higher in the RVO group than in the control group. Carotid plaque (54.3% vs. 28.6%, p = 0.004) was more frequent in the RVO group. Multivariate logistic regression analysis showed that the presence of carotid plaque [odds ratio (OR) 3.15, 95% confidence interval (CI) 1.38–7.16, p = 0.006], as well as smoking, LDL-C level, and baPWV was associated with RVO. Additionally, a multinomial logistic regression model showed that the presence of carotid plaque (OR 3.94, 95% CI 1.65–9.41, p = 0.002) and LDL-C level were associated with branch RVO, whereas smoking and baPWV were associated with central RVO. In conclusion, RVO is associated with subclinical atherosclerosis markers, including carotid plaques and baPWV. These results support the hypothesis of a vascular etiology of RVO and suggest the evaluation of subclinical atherosclerosis in patients with RVO.

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder following diabetic retinopathy and a major cause of visual impairment\(^1\). According to location, RVO is classified into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO)\(^2,3\). The pathogenesis of RVO is still largely unknown. Local factors, such as open-angle glaucoma, systemic conditions, including hypertension, diabetes mellitus, cigarette smoking, and hemostatic abnormalities leading to hypercoagulable states, have been reported as predisposing conditions by several studies\(^4–7\).

Patients with RVO have been reported to have an increased risk of cardiovascular disease and cerebrovascular accident\(^8–11\). Additionally, it has been demonstrated that many risk factors for coronary artery disease and stroke, such as advanced age, hypertension, dyslipidemia, and diabetes mellitus, are associated with RVO\(^1,12–15\). However, the association of subclinical atherosclerosis, an early indicator of atherosclerotic burden and overt cardiovascular disease, and the occurrence of RVO has not been confirmed. Therefore, we investigated the relationship between RVO and markers of subclinical atherosclerosis, including carotid intima-media thickness, carotid plaques, and brachial-ankle pulse wave velocity (baPWV), in patients without established cardiovascular diseases.

Results

After age and sex were matched using propensity scores, 70 patients with RVO and 70 patients without RVO were finally included in the analysis (Fig. 1). Baseline characteristics showed that patients with RVO were older and slightly more obese, had higher total and LDL cholesterol levels, triglyceride levels, 10-year atherosclerotic cardiovascular disease (ASCVD) risks, and lower estimated glomerular filtration rate.
(eGFR) levels than those without RVO in the unmatched cohort. In the matched cohort, patients with RVO had higher total and LDL cholesterol levels than those without RVO, but age, BMI, and eGFR did not differ between the two groups. D-dimer levels did not differ between the two groups in both the matched and unmatched cohorts (Table 1).
### Table 1
Baseline characteristics

|                      | Unmatched Cohort | Matched Cohort |                  |                  |                  |                     |                     |
|----------------------|------------------|----------------|------------------|------------------|------------------|----------------------|----------------------|
|                      | RVO (-)          | RVO (+)        | RVO (-)          | RVO (+)          |                  |                      |                     |
| N                    | N = 175          | N = 70         | N = 70           | N = 70           |                  |                      |                     |
| **Age (years)**      | 54.2 ± 15.1      | 59 ± 10.9      | 0.016            | 0.358            | 58.7 ± 11.4      | 59 ± 10.9           | 0.892               | 0.023              |
| **Female sex n (%)** | 123 (56.2)       | 33 (47.1)      | 0.238            | 0.181            | 33 (47.1)        | 33 (47.1)           | 0.999               | < 0.001            |
| **Hypertension, n (%)** | 169 (77.2) | 60 (85.7) | 0.172            | 0.221            | 55 (78.6)        | 60 (85.7)           | 0.377               | 0.187              |
| **Diabetes mellitus, n (%)** | 27 (12.3) | 12 (17.1) | 0.409            | 0.136            | 13 (18.6)        | 12 (17.1)           | 0.999               | 0.037              |
| **Dyslipidemia, n (%)** | 44 (20.1) | 14 (20) | 0.999            | 0.002            | 12 (17.1)        | 14 (20)             | 0.828               | 0.074              |
| **Smoking, n (%)**   | 54 (24.7)        | 22 (31.4)      | 0.335            | 0.151            | 15 (21.4)        | 22 (31.4)           | 0.25                | 0.228              |
| **Alcohol intake, n (%)** | 73 (33.3) | 27 (38.6) | 0.511            | 0.109            | 24 (34.3)        | 27 (38.6)           | 0.725               | 0.089              |
| **Antiplatelet treatment** | 20 (9.1) | 10 (14.3) | 0.315            | 0.161            | 6 (8.6)          | 10 (14.3)           | 0.425               | 0.18               |
| **BMI (kg/m^2)**     | 24.9 ± 3.6       | 25.7 ± 3       | 0.092            | 0.243            | 24.9 ± 3.3       | 25.7 ± 3            | 0.153               | 0.243              |
| **ASCVD 10 year (%)** | 9.3 ± 10.2       | 12.7 ± 12.1    | 0.022            | 0.302            | 11.1 ± 10.7      | 12.7 ± 12.1         | 0.405               | 0.141              |
| **Glucose level (mg/dL)** | 108 ± 27.7 | 111.8 ± 29.7 | 0.325            | 0.133            | 114.7 ± 33.8    | 111.8 ± 29.7        | 0.59                | 0.091              |
| **HbA1c level (%)**  | 5.7 ± 0.8        | 5.8 ± 0.9      | 0.219            | 0.165            | 5.9 ± 0.9       | 5.8 ± 0.9           | 0.667               | 0.073              |
| **Total cholesterol level (mg/dL)** | 182.7 ± 36 | 199.6 ± 40.1 | 0.001            | 0.445            | 183 ± 36.1      | 199.6 ± 40.1        | 0.011               | 0.435              |
| **Triglyceride level (mg/dL)** | 139.2 ± 71.2 | 156.9 ± 80.1 | 0.08             | 0.234            | 154.1 ± 86.4    | 156.9 ± 80.1        | 0.842               | 0.034              |

ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; RVO, retinal vein occlusion; SMD, standardized mean difference
|                      | Unmatched Cohort | Matched Cohort | Unmatched Cohort | Matched Cohort |
|----------------------|------------------|----------------|------------------|----------------|
| HDL-C level          | 53.5 ± 11.8      | 55.9 ± 19.1    | 0.208            | 0.152          |
| (mg/dL)              |                  |                |                  |                |
| LDL-C level          | 106.2 ± 24.6     | 118.2 ± 30     | 0.001            | 0.44           |
| (mg/dL)              |                  |                |                  |                |
| eGFR (mL/min/1.73 m²)| 98.5 ± 15.4      | 92.5 ± 15      | 0.005            | 0.39           |
| D-dimer level        | 105.7 ± 76.7     | 106 ± 74.9     | 0.973            | 0.005          |
| (ng/mL)              |                  |                |                  |                |
| PWV (cm/second)      | 1485.7 ± 310.7   | 1666.4 ± 321.9| < 0.001          | 0.571          |
|                      |                  |                |                  |                |
| Average ABI          | 1.11 ± 0.1       | 1.14 ± 0.07    | 0.035            | 0.32           |
| CIMT (mm)            | 0.64 ± 0.14      | 0.68 ± 0.12    | 0.033            | 0.307          |
|                      |                  |                |                  |                |
| Carotid plaque, n    |                  |                |                  |                |
| Unilateral           | 37 (16.9)        | 18 (25.7)      | 16 (22.9)        | 18 (25.7)      |
| Bilateral            | 17 (7.8)         | 20 (28.6)      | 4 (5.7)          | 20 (28.6)      |
| Any                  | 54 (24.7)        | 38 (54.3)      | < 0.001          | 0.636          |

ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PWV, pulse wave velocity; RVO, retinal vein occlusion; SMD, standardized mean difference

baPWV and the presence of carotid plaque were higher in patients with RVO than in those without RVO in both the matched and unmatched cohorts. In contrast, carotid intima-media thickness (CIMT) was not different between the two groups in the matched cohort, while the patients with RVO had higher CIMTs than those without RVO in the unmatched cohort (Fig. 2A).

Univariate binary logistic regression models showed that LDL cholesterol levels, baPWV, and the presence of carotid plaques were associated with the occurrence of RVO in the matched cohort. The multivariate binary logistic model showed that ever-smoking, LDL cholesterol level, baPWV, and the presence of carotid plaques were independently associated with the occurrence of RVO, whereas CIMT was not in the matched cohort (Table 2).
Table 2
Logistic regression analysis for predictors of RVO

|                  | Univariate |               |       |          |               |       |          |
|------------------|------------|---------------|-------|----------|---------------|-------|----------|
|                  | OR         | 95% CI        | p-value | OR     | 95% CI        | p-value |
| Age (per 10 years) | 1.02       | 0.76–1.38     | 0.891  | -       | -              | -      |
| Female sex       | 1.00       | 0.51–1.94     | 1.000  | -       | -              | -      |
| Hypertension     | 1.64       | 0.68–3.94     | 0.273  | -       | -              | -      |
| Diabetes mellitus| 0.91       | 0.38–2.16     | 0.825  | -       | -              | -      |
| BMI ≥ 25 kg/m²   | 1.59       | 0.81–3.10     | 0.176  | -       | -              | -      |
| Alcohol intake   | 1.20       | 0.60–2.40     | 0.598  | -       | -              | -      |
| Smoking          | 1.68       | 0.78–3.60     | 0.182  | 2.86    | 1.16–7.04     | 0.022  |
| LDL-C (per 30 mg/dL) | 1.54 | 1.06–2.24     | 0.024  | 1.60    | 1.05–2.44     | 0.030  |
| Carotid IMT (per 0.1 mm) | 1.07 | 0.81–1.41     | 0.648  | -       | -              | -      |
| baPWV (per 5 m/s) | 2.25       | 1.25–4.04     | 0.007  | 2.00    | 1.03–3.89     | 0.041  |

Carotid plaque*

|                  | Univariate |               |       | Multivariate |               |       |
|------------------|------------|---------------|-------|--------------|---------------|-------|
|                  | OR         | 95% CI        | p-value | OR     | 95% CI        | p-value |
| Any              | 2.97       | 1.47–5.98     | 0.002  | 3.15    | 1.38–7.16     | 0.006  |
| Unilateral       | 1.76       | 0.78–3.94     | 0.170  | -       | -              | -      |
| Bilateral        | 7.81       | 2.45–25.0     | 0.001  | -       | -              | -      |

BMI, body mass index; CI, confidence interval; CIMT, carotid intima-media thickness; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; baPWV, brachial-ankle pulse wave velocity

In the 70 patients with RVO, 53 and 16 had BRVO and CRVO, respectively. One patient was classified as either of the RVOs because he was diagnosed with hemi-CRVO. We compared the baseline characteristics of patients with CRVO or those with BRVO with those of the patients without RVO in the matched cohort. Among the three patient groups, diabetes mellitus and dyslipidemia were the most prevalent and hemoglobin A1c levels were highest in the patients with CRVO, whereas total and LDL cholesterol levels were highest in the patients with BRVO. The age, the frequencies of the male sex, ever-smoking, alcohol intake, antiplatelet agents use, BMI, 10-years ASCVD risk, eGFR, and D-dimer levels were not different among the three patient groups (Supplemental Table S1). The presence of carotid plaque and baPWV was higher in patients with BRVO than in those without RVO, whereas they were not different between patients with CRVO and those without RVO (Fig. 2B).

Univariate multinomial logistic regression models showed that LDL cholesterol levels, baPWV, and the presence of carotid plaque were associated with BRVO, whereas ever-smoking and baPWV were
associated with CRVO in the matched cohort. The multivariate multinomial logistic regression model showed that LDL cholesterol level and the presence of carotid plaques were significantly associated with the occurrence of BRVO, whereas ever-smoking was significantly associated and baPWV was marginally associated with the occurrence of CRVO in the matched cohort (Table 3).

**Discussion**

The main findings of this study were as follows: 1) the presence of carotid plaque and baPWV were higher in patients with RVO than in those without RVO; 2) smoking, LDL cholesterol level, baPWV, and the presence of carotid plaques were independently associated with the development of RVO; 3) LDL cholesterol level and the presence of carotid plaques were significantly associated with the development of BRVO, whereas smoking was significantly associated and baPWV was marginally associated with the occurrence of CRVO. To the best of our knowledge, this study is the first to show that the markers for subclinical atherosclerosis, including carotid plaque and baPWV, were associated with the development of RVO.

The pathophysiology of RVO is still unclear, but it is thought that age-related alterations of collagen tissue causing stiffening of the lamina cribrosa and/or atherosclerosis of retinal arteries inducing remodeling and thickening of the arterial wall may cause compression of the adjacent veins within the shared adventitial sheath, leading to blood flow stasis and formation of an endoluminal thrombus. Some studies showed an association with conventional cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking. In this respect, the role of atherosclerosis in the development of RVO is very important, but there is no recommended tool for evaluating atherosclerosis and no rigorous evidence is available concerning the clinical significance of subclinical atherosclerosis in patients with RVO.

Atherosclerosis is a chronic inflammatory disease of the arteries that is the most common pathophysiologic process underlying cardiovascular disease. Atherosclerosis exists along a continuum from subclinical atherosclerosis to clinical atherosclerotic vascular disease, can start early in life, and can remain clinically undetected throughout life until an acute event, such as myocardial infarction or stroke. Subclinical atherosclerosis is an early indicator of atherosclerotic burden, and its timely recognition can slow or prevent the progression to overt cardiovascular disease as well as an optimal approach for primary and secondary prevention of RVO.

Our findings suggest that cardiovascular risk factors and subclinical atherosclerosis are independently associated with RVO, highlighting the close relationship between retinal microvascular abnormalities and systemic atherosclerosis. Furthermore, the differences in the associated predictors between BRVO and CRVO may reflect the differences in pathophysiology between BRVO and CRVO. LDL cholesterol level and the presence of carotid plaques were associated with BRVO, whereas smoking was associated with CRVO in our results. BRVO predominantly occurs at arteriovenous crossing sites where a retinal artery may compress the retinal vein to narrow the lumen. Therefore, retinal artery atherosclerosis plays an
important role in the pathogenesis, and retinal artery atherosclerosis may correlate with atherosclerosis in the carotid arteries. In contrast, CRVO is associated with thrombus formation resulting from endothelial dysfunction in the retinal veins near the lamina cribrosa, where the retinal veins are normally narrowed, which could be easily promoted by smoking\textsuperscript{19,20}. Further studies are needed to determine the exact role of subclinical atherosclerosis in the development of BRVO and CRVO.

In the present study, we documented that the prevalence of carotid plaque was higher in patients with RVO and independently associated with RVO, especially BRVO. Traditionally, carotid plaque and CIMT have been used as surrogate markers for atherosclerotic disease. However, there is debate about the better marker and whether carotid plaques have a stronger association with atherosclerotic disease than CIMT\textsuperscript{21–23}. Previous studies attempted to show evidence of atherosclerosis in patients with RVO, but could not provide definitive evidence of the association because of the lack of a control group or the small number of patients who underwent carotid ultrasound. In 2005, Wong et al. pooled data from two large population-based cardiovascular studies, Atherosclerosis Risk in Communities Study, and the Cardiovascular Health Study, which included 33 patients with BRVO and 6 patients with CRVO\textsuperscript{24}. They showed that about a quarter of participants with RVO (9 of 33) had evidence of carotid plaque on carotid ultrasonography. In addition, carotid plaque was included in the final multivariable model as a significant independent predictor for RVO. However, this study had only 9 patients with RVO and carotid plaque, and was obviously limited by the cross-sectional design. Compared to previous studies, we conducted a case-control study by recruiting patients without RVO, and propensity score matching was used to control for potential confounding variables. Thus, our study suggests a more obvious influence of carotid plaque on the development of RVO, especially BRVO. Further studies are needed to clarify the characteristics of carotid plaques in patients with RVO, and their association with pathophysiology, clinical course, complications, and treatment prognosis.

We also documented that higher baPWV, which is representative of arterial stiffness, was associated with the development of RVO, which supports the hypothesis of a vascular etiology for RVO. Measurement of arterial stiffness is clinically important since arterial stiffness is associated with a patient’s future cardiovascular events, independent of traditional cardiovascular risk factors\textsuperscript{25,26}. There are various methods for measuring arterial stiffness; however, baPWV is non-invasive and relatively simple to measure, making it widely used clinically because measurement of the baPWV requires only wrapping BP cuffs on four extremities. Our results are consistent with those of a previous study by Gouliopoulos et al.\textsuperscript{27}, stating that patients with RVO have increased arterial stiffness by measuring the carotid-femoral pulse wave velocity, and that elevated pulse wave velocity is significantly associated with RVO. However, our data suggest that the role of arterial stiffness is greater in patients with CRVO than in those with BRVO.

This study has several potential limitations. First, it had an observational, single-center design, and may be biased by institutional expertise. Second, although the sample size of patients with RVO was small, we tried to overcome this limitation by propensity score matching. Moreover, although the sample size of
patients with CRVO was relatively small compared to that of patients with BRVO, it has the advantage of presenting the difference between the pathophysiology and risk factors of BRVO and CRVO through subgroup analysis. Third, our control subjects without RVO had more cardiovascular risk factors than the general population because they were recruited in a cardiology outpatient clinic. However, the inclusion of these covariates in the multivariable logistic regression model allowed us to adjust all the risk estimates for their potential confounding effects. Finally, we did not have information on the type of treatment and subsequent follow-up after the episode of RVO; therefore, we could not test the impact of carotid plaque and cardiovascular risk factors on clinical outcome. Future large-scale, population-based, prospective cohort studies on RVO in subjects with carotid plaque could verify whether early atherosclerosis increases the risk of RVO.

In this respect, the role of atherosclerosis in the development of RVO is very important, but there is no established tool for evaluating subclinical atherosclerosis in patients with RVO. Our study suggests that carotid ultrasound may be a good assessment tool to evaluate atherosclerosis and its complications, such as coronary artery disease and stroke, in patients with RVO. In this regard, further studies are needed to clarify the characteristics of carotid plaques in patients with RVO and their association with pathophysiology, clinical course, complications, and treatment prognosis.

In our study, we documented that RVO is significantly associated with subclinical atherosclerosis, represented as carotid plaque and baPWV. Our results support the hypothesis of a vascular etiology of RVO. Evaluating subclinical atherosclerosis may be useful in evaluating cardiovascular risk and tailoring proper management in patients with RVO. Further studies are needed to determine the exact role of subclinical atherosclerosis in the pathogenesis of RVO and to reveal its value in predicting systemic morbidity and mortality in patients with RVO.

Methods

Study design

A prospective, case-control study was conducted in a tertiary referral center. From January 2015 through February 2019, patients diagnosed with RVO in the center were consecutively enrolled in this study. Patients without established ophthalmologic diseases who visited the outpatient clinic of cardiology for cardiovascular disease screening evaluation were enrolled in the control group. Both patients with RVO (RVO group) and those from the control group underwent screening evaluations for clinical cardiovascular diseases through detailed history taking by a cardiologist, laboratory tests, chest radiography, and electrocardiography, and underwent work-ups for subclinical atherosclerosis, including 24-hour ambulatory blood pressure monitoring, carotid ultrasonography, and baPWV measurements. Patients with the following criteria were excluded from both groups: (1) RVO diagnosed more than 12 months prior to enrollment; (2) the presence of any established atherosclerotic cardiovascular diseases, including coronary artery disease and stroke; and (3) the presence of heart failure, malignancy, liver cirrhosis, end-stage renal disease, and systemic autoimmune disease. Written informed consent was
obtained from all patients for review of their medical records. The study was approved by the local ethics review board and conducted in accordance with the Declaration of Helsinki.

**Ophthalmological examination**

A comprehensive ophthalmic examination, including best-corrected visual acuity, refractive errors, intraocular pressure, biomicroscopy, and fundoscopy, was conducted in all patients with RVO. Swept-source optical coherence tomography (DRI OCT Triton, Topcon Corporation, Tokyo, Japan), ultra-wide fundus photography, and fluorescein angiography (Optos California®, Optos PLC, Dunfermline, United Kingdom) were used to confirm the diagnosis and determine the degree of retinal ischemia and the presence of macular edema.

The diagnosis of RVO was determined by retina specialists. Patients with other concomitant ocular diseases (diabetic retinopathy, age-related macular degeneration, uveitis, epiretinal membrane, macular hole in either eye), history of ocular trauma or vitreoretinal surgery, low-quality OCT or fundus images, and high refractive errors (spherical equivalent > ± 6) were excluded.

**Clinical and laboratory evaluation**

Demographic and clinical characteristics, including age, sex, smoking status, and comorbidities, such as hypertension, diabetes mellitus, and dyslipidemia, were obtained through review of medical records. Laboratory test results for lipid profiles, blood glucose level, hemoglobin A1c level, eGFR, and D-dimer level were also collected. Hypertension was defined as the use of antihypertensive medications or an average systolic blood pressure ≥ 130 mmHg and/or average diastolic blood pressure ≥ 80 mmHg in the 24-hour ambulatory blood pressure monitoring (ABPM). Diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin or the level of hemoglobin A1c ≥ 6.5%. The 10-year ASCVD risk was estimated using age, sex, smoking status, total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, systolic blood pressure, and treatment status for hypertension and diabetes mellitus.

**Assessment of subclinical atherosclerosis**

The carotid arteries were assessed using an ultrasound system (IE33; Philips Healthcare, Andover, MA) equipped with an 11 MHz linear array probe. An experienced diagnostic medical sonographer performed CIMT measurements using semi-automated edge-detection software, calculating the mean CIMT value from both common carotid arteries at the end-diastole in a 10-mm segment located 10 mm proximally to the carotid bulb. The mean CIMT of both carotid arteries was used in the study. Carotid plaque was defined as a focal thickening of CIMT > 15 mm or > 50% of the surrounding wall. To evaluate arterial stiffness non-invasively, baPWV and ankle-brachial index (ABI) were measured using an oscillometric sphygmomanometric device (VP-1000 plus; Omron Colin, Kyoto, Japan). The procedure was performed with the patient in a supine position after a 5-minute rest. Cuffs were applied to both brachia and ankles. Blood pressure, pulse volume waveform, and heart rate were obtained simultaneously. ABI was defined as the ratio of the systolic blood pressure at the ankle against the higher systolic blood pressure from either arm. The mean values of the left and right baPWVs and ABI were used in the analysis.
Propensity score matching procedures and statistical analyses

Initially, 123 patients were included in the RVO group and 306 patients were included in the control group. Among the RVO group, six patients with anti-phospholipid syndrome, three patients with severe aortic valve stenosis, one patient with active cancer, and one patient who underwent percutaneous coronary intervention owing to unstable angina were excluded. In addition, 36 patients who had inadequate 24-hour ABPM data were excluded. After patients with any exclusion criteria and those with any missing values in their records were excluded, 76 patients in the RVO group and 175 patients in the control group remained for statistical analysis (Fig. 1).

To reduce the differences in demographics between the two groups caused by the discrepancy in the enrollment during the comparisons of the subclinical atherosclerosis markers, age and sex were balanced between the groups using a propensity score matching procedure. The matching procedure was conducted in a 1:1 ratio using the nearest neighbor method. The quality of the matching procedure was assessed using the absolute mean differences (Supplemental Fig. S1).

Categorical variables were described as numbers (%) and were compared by the chi-squared test. Continuous variables were described as mean ± SD and were compared using Student's t-test. Univariate binary logistic regression analyses were performed to evaluate the associations between clinical factors and the presence of RVO. Multivariate binary logistic regression analyses were used to determine whether an independent association between the subclinical atherosclerosis markers and RVO was evident in the presence of confounding factors. The covariates of the multivariate binary logistic models included age, sex, hypertension, diabetes mellitus, BMI, antiplatelet agents use, alcohol intake, smoking, LDL-C level, baPWV, CIMT, and the presence of carotid plaques. The model was reduced using a backward selection method (cut-off criterion p > 0.05) to avoid overfitting and identify the strong predictors of RVO.

We also conducted another set of analyses consisting of comparisons among the three groups of patients in the matched cohort: with CRVO, with BRVO, and without RVO. Categorical variables were compared among the groups by the chi-squared test, and continuous variables were compared using an analysis of variance. Multinomial logistic regression analyses were performed to compare the differences in the impact of subclinical atherosclerosis markers on the presence of CRVO and BRVO. The same list of variables used in the binary logistic models was also employed as covariates in the multinomial logistic regression analyses. A $p \leq 0.05$ was considered significant. All statistical analyses were performed using the statistical software, R (ver. 4.0; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (ver. 1.3, RStudio Inc., Boston, MA) and their packages, including rms, matchIt, descr, and tableone.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
Declarations

Competing interests
The authors declare no competing interests.

Author Contributions
M.L and Y.L contributed equally to this work and share dual first authorship. M.L and Y.L designed the study, analyzed the data and wrote the main manuscript text. JH.S and Y.U.S designed the study, and supervised the analysis, contributed to the discussion. JH.K contributed to data interpretation and the discussion. BS.K and R.H contributed to data interpretation. H.C contributed to the discussion. all authors reviewed the manuscript.

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