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Relationship between cerebrovascular atherosclerotic stenosis and rupture risk of unruptured intracranial aneurysm: A single-center retrospective study

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ABSTRACT

Objectives: Cerebrovascular atherosclerotic stenosis (CAS) and intracranial aneurysm (IA) have a common underlying arterial pathology and common risk factors, but the clinical significance of CAS in IA rupture (IAR) is unclear. This study aimed to investigate the effect of CAS on the risk of IAR.

Patients and methods: A total of 336 patients with 507 sacular IAs admitted at our center were included. Univariable and multivariable logistic regression analyses were performed to determine the association between IAR and the angiographic variables for CAS. We also explored the differences in CAS in patients aged < 65 and ≥65 years.

Results: In all the patient groups, moderate (50%–70%) cerebrovascular stenosis was significantly associated with IAR (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.8–6.5). Single cerebral artery stenosis was also significantly associated with IAR (OR, 2.3; 95% CI, 1.3–3.9), and intracranial stenosis may be a risk factor for IAR (OR, 1.8; 95% CI, 1.0–3.2). In addition, IAs with lobulation may be at a higher risk for rupture than IAs with regular shape (OR, 2.6; 95% CI, 1.1–5.8; $P = 0.026$), although the same was not true of aneurysms with a daughter sac (OR, 1.8; 95% CI, 0.9–3.7; $P = 0.098$). Bifurcation location (OR, 2.4; 95% CI, 1.5–3.8; $P < 0.001$) was significantly associated with aneurysmal rupture. For the patient subgroup aged < 65 years, rupture risk was higher for aneurysms with moderate stenosis (OR, 3.4; 95% CI, 1.8–6.5). For patients aged ≥65 years, single-artery stenosis (OR, 1.9; 95% CI, 1.2–3.0) was statistically associated with IAR.

Conclusions: We observed substantial differences in the severity of atherosclerotic stenosis, parent-artery stenosis, number of stenotic arteries, and intracranial/extracranial stenosis as indicators between ruptured and unruptured aneurysms. CAS is significantly associated with the risk of intracranial aneurysm rupture, whether in patients aged ≥65 years or < 65 years. These findings indicate the clinical significance of CAS in IAR.

1. Introduction

Despite endovascular and microsurgical advances in early interventions for intracranial aneurysms (IA), the risk of treatment-related unfavorable outcomes, including death, is reported to be 3.9%–9.0%. [1,2] However, the annual rupture risk of an unruptured IA (UIA) is 0.95%–1.4% [3]. Therefore, once a UIA is diagnosed, the risk of rupture should be weighed against the risk of treatment, emphasizing the need for criteria to predict rupture in clinical decision-making. However, despite intense investigations, our understanding of the mechanisms leading to aneurysm development, progression, and rupture remains incomplete. In a systematic review on the prevalence of incidental IAs, atherosclerotic diseases appeared to increase the risk of incidental IAs [4]. However, the relationship between cerebrovascular atherosclerotic stenosis (CAS) and the rupture risk of IAs remains unclear.

IA is the result of degeneration of the arterial wall, and CAS is characterized by hyperplasia of the vascular wall. The pathological outcomes of the two conditions are different, but there are some similar pathways involved in their formation and development. The pathological changes in IA and AS show some similar features, such as early vascular endothelial injury, imbalance of vascular smooth muscle cell proliferation and apoptosis, and inflammatory response. [5,6] The possible association of IA with inflammation and the critical role of inflammation in the pathogenesis of atherosclerosis could serve as the

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common link between IA and atherosclerosis, indicating an association between IAs and CAS [7,8]. An accumulating body of evidence has implicated inflammation as a critical contributor to aneurysm pathogenesis, and atherosclerosis is a common pathological feature in saccular IA. Several studies have shown atherosclerotic changes within the aneurysm wall. Killer-Oberpfalzer et al. [9] and Kosierkiewicz et al. [10] found that atherosclerotic lesions were present in all saccular IAs. Larger aneurysms contain advanced atherosclerotic lesions with phenotypically modulated smooth muscle cells, lipid-laden macrophages, and lymphocytes. [9] Additionally, progression of atherosclerosis is positively correlated with aneurysmal growth [10,11]. With their common vascular risks, such as hypertension and smoking, the pathogenic mechanisms underlying atherosclerosis are also fundamentally involved in IA rupture (IAR). However, very few studies have directly investigated the association between CAS and the risk of IAR.

We hypothesized that CAS differences exist between ruptured IA (RIA) and UIA. In this study, a subgroup of patients with IAs was analyzed to characterize the features of atherosclerotic stenosis in RIAs relative to those in UIAs. This was done to characterize the predictors of aneurysmal rupture and further our understanding of IAs.

2. Patients and methods

This was a single-center and retrospective study. We retrospectively reviewed records of consecutive patients with IAs who attended our hospital from September 2011 to September 2018. All the patients of this study were screened from the patients who underwent digital subtraction angiography (DSA) or endovascular treatment at our hospital. All angiographic variables for IA and cerebrovascular atherosclerotic stenosis were evaluated based on the patient's initial two/three-dimensional DSA images. We divided IAs and patients into ruptured and unruptured groups based on whether the aneurysm was ruptured at admission. All patients presented with SAH caused by a ruptured aneurysm. SAH diagnoses were confirmed with computed tomography (CT) scans, CSF analysis, or intraoperatively by a neurosurgeon. Our exclusion criteria included: (1) dissecting, fusiform, traumatic, mycotic, or partially thrombosed aneurysms; (2) Patients without complete DSA data or without readable and clear three-dimensional rotational angiography that allowed an evaluation of lesion geometry and morphology; (3) aneurysms associated with cerebral arteriovenous malformation, arteriovenous fistula, or moyamoya disease.

We received the approval of our institutional review board to conduct this study, and obtained informed consent from all patients or their families. Reporting guidelines of the STROBE statement have been implemented in this manuscript.

We obtained information on patient characteristics, including age, sex, and comorbid conditions, including hypertension, heart comorbidities (coronary artery disease, myocardial infarction), hypercholesterolemia, and diabetes mellitus. Information regarding comorbid conditions was obtained from patient self-reporting and/or available medical records. Hypertension, hypercholesterolemia, and diabetes mellitus were defined as present if the patient or medical records indicated hypertension, hypercholesterolemia, or hyperglycemia for which either drug treatment, lifestyle modification, or other advice had been provided. Current smokers were defined as patients who smoked at the time of treatment or smoked ≥100 cigarettes during the past one year. Former smokers were defined as patients who had smoked ≥100 cigarettes but had not smoked during the past year. [12] Alcohol use was defined as ongoing alcohol consumption.

The diagnosis of morphological features and stenosis was determined with imaging studies according to 2D/3D DSA by three experienced readers who worked at our center. There were three interventional neuroradiologists (DM W, LJ W, and P Q, with more than 10 years of experience). Each reader made his own morphological assessment independently and the final assessment was determined by results agreed by two or three readers.

Angiographic variables for cerebrovascular stenosis included the most severe atherosclerotic stenosis (less than 50%/50%–70%/70% or more), number of stenotic arteries (single/multiple), parent-artery stenosis (less than 50%/50–70%/70% or more), and intracranial or extracranial stenosis. Severity of atherosclerotic stenosis was defined as the highest severity of stenosis among all cerebral arteries. We collected information for both intracranial stenosis and extracranial arteries (extracranial segment of the internal carotid artery and vertebral artery). Extracranial artery stenosis was determined as 50% or more stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, [13] based on interactive reformations perpendicular and parallel to the internal carotid artery. The anatomic severity of intracranial artery stenotic lesions was determined as 50% or more according to the Warfarin–Aspirin Symptomatic Intracranial Disease method [14].

For aneurysm morphology, irregular morphology was defined as any one of three morphological features: daughter sac, lobulation, and other irregular shape of the aneurysm. 'Daughter sac' was defined as an irregular protrusion of the aneurysm wall or a separate protuberance arising from the margin sac that was less than 25% of the total volume of the sac on 3D images from DSA. Lobulation was defined as a protuberance arising directly from the primary neck of the aneurysm or from the main body and representing 25% or more of the apparent volume of the main sac. [26] Other irregular shapes were defined as irregular shapes other than DS and lobulation, such as tapered, polygonal, elongated, etc. We also measured aneurysm size, aspect ratios (AR), and location. The AR was defined as the height of the aneurysm compared to its average aneurysmal neck size. Bifurcation location was considered as aneurysms located at parent artery bifurcations (internal carotid artery terminus, anterior/posterior communicating artery, middle cerebral artery bifurcation, and basilar artery tip).

2.1. Statistical analyses

Demographic, clinical, and radiological data were first assessed in univariable analysis comparing patients with SAH to those with unruptured aneurysms. Variables for multivariable analysis were chosen on the basis of univariable analysis. As predetermined, variables with a $P < 0.20$ in the univariate analysis were evaluated in our multivariate analysis. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS Statistics for Windows (Version 23.0; IBM Corp, Armonk, NY, USA).

3. Results

3.1. Study population

A total of 468 patients with 638 IAs were evaluated or treated at our institution during the study period. After applying our exclusion criteria, a total of 336 patients with 507 sacular IAs were included (age range: 17–90 years), including 121 ruptured IAs and 386 unruptured IAs. The flow chart showing the inclusion of study population is shown in Fig. 1. The mean age was 59.5 ± 12.1 years in the unruptured IA group and 59.4 ± 11.2 years in the ruptured IA group.

3.2. Factors related to IAR in all patients

Among the 336 patients with IAs, 84 (25%) showed moderate or severe CAS (50% or more), including 31 (9.2%) with moderate stenosis (50%–70%), and 53 (15.8%) with severe stenosis (70% or more). The demographic data and main aneurysm characteristics of both groups are summarized in Table 1.

The following covariates met our previously determined level of significance and entered the stepwise forward selection for the unconditional logistic model: sex ($P = 0.099$), age ≥50 years ($P = 0.115$), smoking status ($P = 0.059$), hyperlipidemia ($P = 0.099$), diabetes

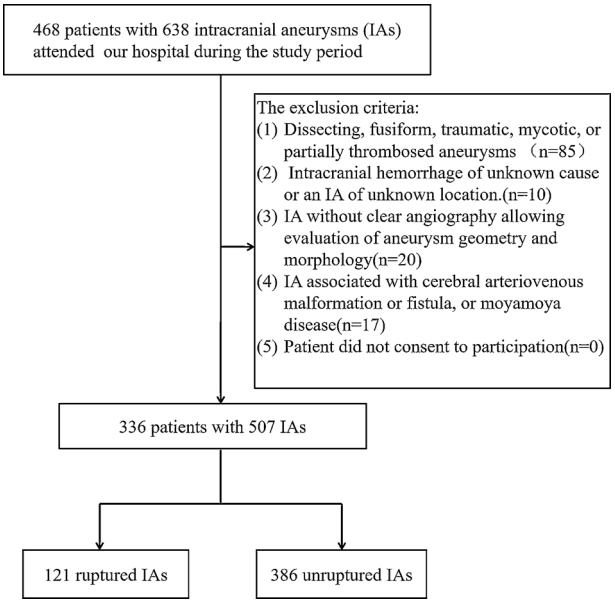

Fig. 1. The flow chart of study.

mellitus ($P = 0.015$), history of SAH ($P = 0.187$), heart comorbidities ($P = 0.031$), irregular shape ($P = 0.009$), bifurcation location ($P < 0.001$), location of the posterior circulation artery ($P = 0.098$), and severity of atherosclerotic stenosis ($P < 0.001$).

After adjusting for sex, age, smoking status, hyperlipidemia, diabetes mellitus, history of SAH, heart comorbidities, irregular shape, bifurcation location, location of posterior circulation artery, and the most severe atherosclerotic stenosis, the multivariate analysis indicated that the risk was more than three times higher in aneurysms with 50%–70% CAS (OR, 3.4; 95% CI, 1.8–6.5; $P < .001$) than in IAs with no or less than 50% intracranial/extracranial stenosis, although the association between 70% or higher CAS and IAR was not statistically significant.

We also entered the number of stenotic arteries ($P = 0.002$) and intracranial/extracranial stenosis ($P = 0.185$) into the conditional logistic regression model. The results showed that single-artery stenosis was significantly associated with aneurysmal rupture (OR, 2.3; 95% CI, 1.3–3.9; $P = 0.003$), but the association between multiple-artery stenosis and IAR was not statistically significant (OR, 0.5; 95% CI, 0.2-21.; $P = 0.465$). Intracranial stenosis may be a risk factor for IAR (OR, 1.8; 95% CI, 1.0–3.2; $P = 0.046$), but extracranial stenosis (OR, 1.5; 95% CI, 0.7–3.3; $P = 0.340$) was not related to IAR.

In addition, IAs with lobulation may be at a higher risk for rupture than IAs with regular shape (OR, 2.6; 95% CI, 1.1–5.8; $P = 0.026$), although the same was not true of aneurysms with a daughter sac (OR, 1.8; 95% CI, 0.9–3.7; $P = 0.098$). Bifurcation location (OR, 2.4; 95% CI, 1.5–3.8; $P < 0.001$) was significantly associated with aneurysmal rupture (Table 1).

3.3. Factors related to IAR in patients aged < 65 years

A total of 232 patients aged 64 years or less presented with 328 IAs, including 251 UIAs and 77 RIAs. The mean age was 52.9 ± 9.4 years in the UIA group and 52.7 ± 7.7 years in the RIA group. The demographics and main aneurysm characteristics of both groups are shown in Table 2. The following covariates met our previously determined level of significance and entered the unconditional logistic model: female sex ($P = 0.180$), diabetes mellitus ($P = 0.068$), history of SAH ($P = 0.054$), heart comorbidities ($P = 0.031$), irregular shape ($P = 0.054$), bifurcation location ($P < 0.001$), and the most severe atherosclerotic stenosis ($P = 0.002$). The multivariate analysis indicated that the risk was 3.8 times higher in aneurysms with 50%–70% CAS (OR, 3.4; 95% CI, 1.8–6.5; $P < 0.001$) than in IAs with no or less than 50% intracranial/extracranial stenosis, while the association between 70% or greater CAS and IAR was not statistically significant (OR, 0.3; 95% CI, 0.1–1.0; $P < 0.001$). We sequentially entered the number of stenotic arteries ($P = 0.002$) and intracranial/extracranial stenosis ($P = .185$) into the conditional logistic regression model and found that both of these may not be significantly associated with IAR. In addition, bifurcation location (OR, 3.5; 95% CI, 2.0–6.3; $P < 0.001$) significantly increased the risk of aneurysmal rupture (Table 2).

3.4. Factors related to IAR in patients aged ≥65 years

The study population included 104 patients aged 65 years or older (age range: 65–90 years) with 179 IAs, including 135 UIAs and 44 RIAs. The demographic data and main aneurysm characteristics are shown in Table 3. The following covariates met our previously determined level of significance and entered the unconditional logistic model: hyperlipidemia ($P = 0.081$), diabetes mellitus ($P = 0.097$), heart comorbidities ($P = 0.031$), irregular shape ($P = 0.012$), location of posterior circulation ($P = 0.103$), bifurcation location ($P = 0.051$), and severity of atherosclerotic stenosis ($P = 0.034$). The multivariate analysis indicated that the severity of CAS was not statistically associated with IAR. We respectively entered the number of stenotic arteries ($P = 0.018$) into the logistic regression model and found that the risk was 1.9 times higher in aneurysms with single-artery stenosis (OR, 1.9; 95% CI, 1.2–3.0; $P = 0.010$) while the association between multiple-artery stenosis and IAR was not statistically significant (OR, 0.6; 95% CI, 0.2–1.7; $P = 0.369$).

In addition, IAs with a daughter sac may be at a higher risk for rupture than IAs with a regular shape (OR, 4.7; 95% CI, 1.5–14.5; $P = 0.008$), although similar results were not obtained for aneurysms with lobulation (OR, 3.7; 95% CI, 0.7–19.1; $P = 0.119$).

3.5. Atherosclerotic stenosis characteristics in patients aged < 65 years and those aged ≥65 years

Of the 507 IAs included, 328 (64.7%) aneurysms were in patients aged < 65 years, and 179 (35.3%) aneurysms were in those aged ≥65 years. Atherosclerotic stenosis characteristics in the two groups are presented in Table 4. The angiographic variables for atherosclerotic stenosis that showed significant differences ($P < 0.001$) between the two groups included the most severe atherosclerotic stenosis (less than 50%/50–70%/70% or more), number of stenotic arteries (single/multiple), parent-artery stenosis (less than 50%/50–70%/ 70% or more), and intracranial or extracranial stenosis.

4. Discussion

The relationship between cerebrovascular atherosclerotic stenosis (CAS) and the rupture risk of IAs has not been clarified to date. In this large observational study, we showed that 25% of the patients with IAs had moderate or severe CAS, and different degrees of CAS may be independently associated with higher risks of aneurysmal SAH. In addition, stenosis of the parent artery may be more likely in older patients and the number of cases showing CAS in the older group was greater than that in the younger group.

4.1. Interpretation

Although it is still unclear whether inflammation is the cause of IAR or just a reaction to the underlying cause of the degenerative remodeling that predisposes aneurysms to rupture, histopathological studies have shown that inflammation is clearly an indicator of a degenerated, rupture-prone aneurysm wall. Atherosclerosis is usually

Table 1
Summary of Statistical Data for All Patients with Ruptured and Unruptured Intracranial Aneurysms.

	UIA n(%)	RIA n(%)	*P* value of Univariate Analysis	*P* value of Multivariate Analysis	OR (95% CI)
N	386	121			
Female	236(61.1%)	84(69.4%)	0.099		
Age(years)	59.5 ± 12.1	59.4 ± 11.2	0.962		
≧50	324(89.3%)	94(77.7%)	0.115		
Smoking					
No	289(74.9%)	100(82.6%)	0.059		
Current Smoking	84(21.8%)	21(17.4%)			
Former Smoking	13(3.4%)	0			
Alcohol use	46(11.9%)	13(10.7%)	0.725		
Hypertension	252(65.3%)	72(59.5%)	0.248		
Hyperlipidemia	84(21.8%)	18(14.9%)	0.099		
Diabetes mellitus	54(14.0%)	7(5.8%)	0.015	0.015	0.3(0.1–0.8)
History of SAH	22(5.7%)	11(9.1%)	0.187		
Heart comorbidities	54(87.1%)	8(12.9%)	0.031		
Bifurcation location	169(43.8%)	81(66.9%)	< 0.001	< 0.001	2.4(1.5–3.8)
Irregular shape					
Regular	291(75.4%)	69(57.5%)	< 0.001	Reference	Reference
Irregular	51(13.2)	23(19.2)		0.095	1.6(0.9–2.9)
Daughter sac	28(7.3%)	16(13.3)		0.098	1.8(0.9–3.7)
Lobulation	16(4.1%)	12(10%)		0.026	2.6(1.1–5.8)
Size, mm	5.9 ± 6.1	5.5 ± 4.0	0.463		
≥5	101 (26.2%)	25(20.7%)	0.221		
Multiple aneurysm	221(57.3%)	63(52.1%)	0.316		
AR	1.29 ± 0.86	1.35 ± 0.73	0.493		
≥1.35	111(28.8%)	49(33.9%)	0.283		
Location					
ICA	190(49.5%)	31(25.6%)	< 0.001		
ACOMA	47(12.2%)	20(16.5%)			
PCOMA	44(11.4%)	26(21.5%)			
ACA	14(3.6%)	4(3.3%)			
MCA	49(12.7%)	21(17.4%)			
PC	41(10.6%)	19(16.7%)			
Location of PC	42(10.9%)	20(16.5%)	0.098	0.016	2.2(1.2–4.1)
Severity of Atherosclerosis stenosis					
Less than 50%	297(76.9%)	87(71.9%)	< 0.001	Reference	Reference
50-70%	13(5.2%)	11(15.6%)		< 0.001	3.4(1.8–6.5)
70 or more	32(12.7%)	3(3.9%)		0.242	0.7(0.3–1.3)
Stenosis of parent artery					
Less than 50%	366(94.8%)	115(95.0%)	0.579		
50-70%	12(3.1%)	5(4.1%)			
70% or more	8(2.1%)	1(0.8%)			
Number of stenotic arteries					
No	297(76.9%)	87(71.9%)	0.002	Reference	Reference
Single	48(12.4%)	29(24.0%)		0.003	2.3(1.3–3.9)
Multiple	41(10.6%)	5(4.1%)		0.465	0.5(0.2–1.2)
Intracranial / extracranial stenosis					
No	297(76.9%)	87(71.9%)	0.185	Reference	Reference
Intracranial stenosis	46(11.9%)	22(18.2%)		0.046	1.8(1.0–3.2)
Extracranial stenosis	27(7.0%)	10(8.3%)		0.340	1.5(0.7–3.3)
Intracranial and extracranial stenosis	16(4.1%)	2(1.7%)		0.412	0.4(0.1–1.9)

considered a chronic inflammatory disease since inflammation plays an important role in all stages of the atherosclerotic process. [15,16] Therefore, the possible association of IA with atherosclerosis and the critical role of inflammation in the pathogenesis of atherosclerosis could provide a common link between IA and inflammation [17]. Several studies have investigated various aspects of the inflammatory response as contributors in producing reactive oxygen species, up-regulating surface adhesion molecules and cytokines in the vessel wall, and increasing luminal permeability. These inflammatory infiltrates can produce large amounts of matrix metalloproteinases that degrade the extracellular matrix, thus inducing degradative processes and driving intracranial aneurysm growth and rupture [18]. Such inflammatory infiltrates also promote the formation of atherosclerotic plaques [19,20]. The pathogeneses of both atherosclerosis and IA include leukocytes, complement, immunoglobulins, cytokines, and differential expression of genes involved with immune response/inflammation. Preliminary data suggest that therapies targeting the inflammatory response may be effective for IA.

IA formation (and rupture) and CAS are all chronic diseases, and their development is a long-term process, and it is difficult to come to the conclusion of who comes first in this population. However, recent advancements in imaging and other technologies have improved our understanding of the inflammation process affecting aneurysmal rupture; e.g., aneurysm wall enhancement on vessel wall magnetic resonance imaging (VW-MRI) may be a potential marker for wall inflammation, demonstrating enormous potential in providing new risk stratification parameters [21–23]. Shimonaga et al. [22,23] evaluated aneurysms using VW-MRI and characterized these with histopathological assessments, and they found that wall thickening accompanied by atherosclerosis, neovascularization, and macrophage infiltration corresponded to visualization of the aneurysm wall using native VWI and to aneurysm wall enhancement. However, few studies have specifically and systematically studied the association between IAR and atherosclerotic stenosis.

In main analysis of all our cases, multivariate analysis indicated that aneurysms with 50%–70% of CAS were associated with a higher risk of IAR. In addition, single-artery stenosis and intracranial stenosis significantly increased the risk of aneurysmal rupture. These findings

Table 2
Summary of Statistical Data for Patients Aged 64 Years or Less with Ruptured and Unruptured Intracranial Aneurysms.

	UIA n(%)	RIA n(%)	*P* value of Univariate Analysis	*P* value of Multivariate Analysis	OR (95% CI)
n	251	77			
Female	113(45.0%)	28(36.4%)	0.180		
Age(years)	52.9 ± 9.4	52.7 ± 7.7	0.861		
Smoking					
No	186(74.1%)	63(81.8%)	0.217		
Current Smoking	59(23.5%)	14(18.2%)			
Former Smoking	6(2.4%)	0			
Alcohol use	41(16.3%)	11(14.3%)	0.667		
Hypertension	152(60.6%)	41(53.2%)	0.254		
Hyperlipidemia	41(16.3%)	10(13.0%)	0.478		
Diabetes mellitus	27(10.8%)	3(3.9%)	0.068		
History of SAH	18(7.2%)	11(14.3)	0.054		
Heart comorbidities	54(87.1%)	8(12.9%)	0.031		
Bifurcation location	115(45.8%)	56(72.7%)	< 0.001	< 0.001	3.5(2.0–6.3)
Irregular shape					
Regular	190(75.7%)	48(62.3%)	0.054		
Inregular	20(14.8%)	11(25.6%)			
Daughter sac	19(7.6%)	8(10.4%)			
Lobulation	11(4.4%)	9(11.7%)			
Size, mm	5.6 ± 4.8	5.3 ± 3.8	0.639		
≥5	103 (41.0%)	35(45.5%)	0.492		
Multiple aneurysm	127(50.6%)	36(46.8%)	0.555		
AR	1.32 ± 0.85	1.46 ± 0.83	0.180		
≥1.46	68(27.1%)	25(32.5%)	0.360		
Location					
ICA	120(47.8%)	14(18.2%)	< 0.001		
ACOMA	34(13.5%)	18(23.4%)			
PCOMA	27(10.8%)	17(22.1%)			
ACA	9(3.6%)	4(5.2%)			
MCA	37(14.7%)	14(18.2%)			
PC	24(9.6%)	10(13%)			
Location of PC	226(90.0%)	67(87.0%)	0.452		
Severity of Atherosclerosis stenosis					
Less than 50%	206(82.1%)	62(80.5%)	0.002	Reference	reference
50-70%	13(5.2%)	11(15.6%)		0.003	3.8(1.6–9.2)
70 or more	32(12.7%)	3(3.9%)		0.050	0.3(0.1–1.0)
Stenosis of parent artery					
Less than 50%	244(97.2%)	76(98.7%)	0.536		
50-70%	4(1.6%)	0			
70 or more	3(1.2%)	1(1.3%)			
Number of stenosis arteries					
No	206(82.1%)	62(80.5%)	0.094	Reference	Reference
Single	22(8.8%)	12(15.6%)		0.098	1.9(0.9–4.3)
Multiple	23(9.2%)	3(3.9%)		0.189	0.4(0.1–1.5)
Intracranial / extracranial stenosis					
No	206(82.1%)	62(80.5%)	0.027	Reference	Reference
Intracranial stenosis	23(9.2%)	14(18.2%)		0.091	1.9(0.9–4.0)
Extracranial stenosis	11(4.4%)	1(1.3%)		0.454	10.6(0.1–3.7)
Intracranial and extracranial stenosis	11(4.4%)	0		–	–

revealed the possible association between IAR and atherosclerosis, and the critical role of inflammation in the pathogenesis could provide a common link between IAR and atherosclerosis. Interestingly, a large case-control study [24] showed a significant association between aspirin use and a decreased risk of IAR and a significant inverse dose-response relationship between aspirin dose and IAR. Recently, the International Study of Unruptured Intracranial Aneurysms investigators reported that patients who used aspirin at least three times weekly had significantly lower risks of aneurysm rupture than those who never used aspirin. [25] Their research is consistent with our findings, and one possible mechanism by which aspirin may exert its preventive effects on IAR could be by stabilizing aneurysm walls and counteracting the proinflammatory pathways for atherosclerosis. However, aneurysms with 70% or greater CAS and multiple-artery stenosis were likely related to a decreased risk of IAR. One possible explanation is that these patients are more prone to cerebral ischemic events, so an aneurysm is detected before the aneurysm ruptures.

In this study, stenosis of the parent artery was more likely to be found in older patients (≥ 65 years), and the difference between the two age groups was significant (P = .001). However, the association between parent-artery stenosis and IAR was not statistically significant in the entire population and in the different age groups. This result may be related to hemodynamic changes such as reduced blood flow in the stenotic parent artery.

4.2. Differences of CAS in different age groups

We also explored the differences in CAS in different age groups (< 65 and ≥ 65 years), and 44.2% and 55.8%, respectively, of the younger and elderly patients had moderate stenosis (50%–70%). However, for severe stenosis, the result was exactly the opposite. Similarly, for the younger age group, the rupture risk was 1.9 times higher in aneurysms with moderate stenosis compared to that in IAs with no or less than 50% stenosis, while the association between severe stenosis and IAR was not statistically significant. We respectively entered the number of stenotic arteries and intracranial/extracranial stenosis into the conditional logistic regression model and found that both may not be significantly associated with IAR.

In the younger age group, the presence of aneurysms with single-artery stenosis and extracranial stenosis was statistically associated

Table 3
Summary of Statistical Data for Patients Aged 65 Years or More with Ruptured and Unruptured Intracranial Aneurysms.

	UIA n(%)	RIA n(%)	*P* value of Univariate Analysis	*P* value of Multivariate Analysis	OR (95% CI)
n	135	44			
Female	37(27.4%)	9(20.5%)	0.359		
Age(years)	71.6 ± 5.6	71.1 ± 4.9	0.558		
≧50	31(23.0%)	10(22.7%)	1.000		
Smoking					
No	103(76.3%)	37(84.1%)	0.264		
Current Smoking	25(18.5%)	7(15.9%)			
Former Smoking	7(5.2%)	0			
Alcohol use	5(3.7%)	2(4.5%)	0.802		
Hypertension	100(74.1%)	31(70.5%)	0.638		
Hyperlipidemia	43(31.9%)	8(18.2%)	0.081		
Diabetes mellitus	27(20.0%)	4(9.1%)	0.097		
History of SAH	4(3.0%)	0	0.248		
Heart comorbidities	54(87.1%)	8(12.9%)	0.031	0.007	0.1(0.0–0.6)
Bifurcation location	54(40.0%)	25(56.8%)	0.051		
Irregular shape					
Regular	101(74.8%)	21(48.8%)	0.012	Reference	Reference
Inregular	20(14.8%)	11(25.6%)		0.099	2.9(0.9–5.6)
Daughter sac	9(6.7%)	8(18.6%)		0.008	4.7(1.5–14.5)
Lobulation	5(3.7%)	3(7.0%)		0.119	3.7(0.7–19.1)
Size, mm	6.6 ± 8.1	5.8 ± 4.4	0.529		
≥5	57 (42.2%)	22(50.0%)	0.367		
Multiple aneurysm	94(69.6%)	27(61.4%)	0.309		
AR	1.25 ± 0.88	1.16 ± 0.46	0.519		
≥1.35	111(28.8%)	49(33.9%)	0.283		
Location					
ICA	71(52.6%)	17(38.6%)	0.139		
ACOMA	13(9.6%)	2(4.5%)			
PCOMA	17(12.6%)	9(20.5%)			
ACA	6(3.7%)	0			
MCA	12(8.9%)	7(15.9%)			
PC	17(12.6%)	9(20.5%)			
Location					
AC	118(87.4%)	34(77.3%)	0.103		
PC	17(12.6%)	10(22.7%)			
Severity of atherosclerosis stenosis					
Less than 50%	91(67.4%)	25(56.8%)	0.034		
50-70%	13(9.6%)	11(25.0%)			
70 or more	31(23.0%)	8(18.2)			
Stenosis of parent artery					
Less than 50%	122(90.4%)	39(88.6%)	0.224		
50-70%	8(5.9%)	5(11.4%)			
70 or more	5(3.7%)	0			
Number of stenotic arteries					
No	91(67.4%)	25(56.8%)	0.018	Reference	Reference
Single	26(19.3%)	17(38.6%)		0.010	1.9(1.2–3.0)
Multiple	18(13.3%)	2(4.5%)		0.369	0.6(0.2–1.7)
Intracranial/extracranial stenosis					
No	91(67.4%)	25(56.8%)	0.490		
Intracranial stenosis	23(17.0%)	8(18.2%)			
Extracranial stenosis	16(11.9%)	9(20.5%)			
Intracranial and extracranial stenosis	5(3.7%)	2(4.5%)			

with IAR, while the severity of cerebrovascular stenosis, multiple-artery stenosis, and intracranial stenosis were not. For different indicators of cerebral vascular atherosclerotic stenosis, although the results are inconsistent in the different age groups and the overall study population, atherosclerotic stenosis was still shown to affect the risk of aneurysm rupture. In addition, the role of age in patients with aneurysms with stenosis and patients with a simple aneurysm or stenosis may not be the same, which requires a further prospective multicenter study with a larger sample.

4.3. Limitations

There are some limitations in our study. First, this was a retrospective, single-center study, so the conclusions are limited and additional evaluations are required to yield more evidence to confirm the association between IAR and atherosclerosis. Second, we only balanced the risk factors based on previous studies. However, there may be some potential risk factors that affect IAR risk that are not included in this study. Third, we considered four factors, namely, the most severe atherosclerotic stenosis, parent-artery stenosis, number of stenotic arteries, and intracranial/extracranial stenosis as indicators for assessing cerebral vascular atherosclerotic stenosis, but this approach may still lack sufficient persuasiveness and typicality to clarify the relationship between IAR and atherosclerotic stenosis, hence, more prospective data or related scoring models may be needed in future.

5. Conclusions

We observed substantial differences in the most severe atherosclerotic stenosis, parent-artery stenosis, number of stenotic arteries, and intracranial/extracranial stenosis as indicators between ruptured and unruptured aneurysms. These findings support the potential protective effect of anti-inflammatory agents and statins and may justify randomized prevention trials in patients with unruptured aneurysms. In

Table 4
Atherosclerosis stenosis characteristics in < 65 years group and ≥65 years group.

	< 65 years n(%)	≥65 years n (%)	*P* value
n	328	179	
Stenosis of atherosclerosis stenosis			
Less than 50%	268(81.7%)	116(64.8%)	< 0.001
50-70%	25(7.6%)	24(13.4%)	
70 or more	35(10.7%)	39(21.8%)	
Stenosis of parent artery			
Less than 50%	320(97.6%)	161(89.9%)	< 0.001
50-70%	4(1.2%)	13(7.3%)	
70 or more	4(1.2%)	5(2.8%)	
Number of cerebralvascular stenosis			
No	268(81.7%)	116(64.8%)	< 0.001
Single	34(10.4%)	43(24.0%)	
Multiple	26(4.9%)	20(11.2%)	
Intracranial / extracranial stenosis			
No	246(81.7%)	116(64.8%)	< 0.001
Intracranial stenosis	37(11.3%)	31(17.3%)	
Extracranial stenosis	12(3.7%)	25(14%)	
Intracranial and extracranial stenosis	11(3.4%)	7(3.9)	

addition, aneurysms with severe atherosclerotic stenosis and multiple-artery stenosis were likely related to decrease IAR.

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Contributorship statement

Acquisition of data: all authors. Analysis and interpretation of data: XF and DW. Drafting of the article: XF and DW. Critical revision of the article: all authors.

Data sharing statement

All available data can be obtained by contacting the corresponding author

Declaration of Competing Interest

None declared.

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