Original Article

Intracranial aneurysm rupture risk in northern China: a retrospective case-control study

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Background: Rupture of intracranial aneurysms (IAs) can cause subarachnoid hemorrhage (SAH), which leads to severe neurological dysfunction and even death. Exploring the risk factors for IA rupture and taking preventive measures accordingly can reduce or prevent the occurrence of SAH. Currently, there is still no consensus on the detrimental factors for IA rupture. Thus, our study aimed to investigate the risk factors of IA rupture in a population of northern China.

Methods: We systematically collected the demographic features, medical history, and imaging data of aneurysms from patients with ruptured and unruptured IAs (UIAs) who attended the Department of Neurosurgery at the Second Hospital of Hebei Medical University from 2014 to 2019. All cases had been diagnosed by digital subtraction angiography. We excluded patients with SAH resulting from injuries, as well as those with vascular dissection and incomplete data. Finally, 1,214 patients including 616 with ruptured IAs and 598 with UIAs were collected for further analysis. A case-control study was conducted, in which multivariable logistic regression was used to analyze the risk factors for IA rupture.

Results: Our multivariable logistic regression showed that anterior cerebral artery [odds ratio (OR) =2.413; 95% confidence interval (CI): 1.235–4.718], anterior communicating artery (OR =3.952; 95% CI: 2.601–6.006), posterior communicating artery (OR =2.385; 95% CI: 1.790–3.177), and anterior circulation branches (OR =3.493; 95% CI: 1.422–8.581) were risk factors for IA rupture, whereas patients with a history of cerebral infarction (OR =0.395; 95% CI: 0.247–0.631) and those with IAs located in the internal carotid artery (OR =0.403; 95% CI: 0.292–0.557) were less likely to have IA rupture.

Conclusions: IAs at specific locations are prone to rupture. These IAs should be paid particular attention and preventive measures should be taken to reduce or prevent their rupture.

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Keywords: Rupture of intracranial aneurysms (ruptured IAs); unruptured intracranial aneurysms (UIAs); risk factors; location

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Introduction

Intracranial aneurysms (IAs), a vascular disorder involving a cystic protuberance caused by local thinning of the vascular wall, mainly manifest as localized expansions of the intracranial arterial wall that might rupture and subsequent bleeding. The prevalence of IAs is approximately 3% in the general population (1,2). About 0.2–2.4% of IA cases will have IA rupture, which leads to subarachnoid hemorrhage (SAH) (3-5), with a high mortality of more than 30% (6), SAH severely damages neurological function, imposing a heavy economic burden on families and society (7). Therefore, identifying the influential factors for IA rupture, evaluating the rupture risk, and taking effective preventive measures are critical to reducing or preventing IA rupture.

Previous studies have reported that gender, age, the specific complications of IA patients, as well as the size, location, and shape of IAs are the influential factors of IA rupture (8,9). Reports have highlighted that rupture rates were different in different regions, which might have been due to the different demographic characteristics of populations in different regions (10). Results have been inconsistent due to the diverse populations, different sample sizes, and different research measures of these studies (11,12). It is noteworthy that IAs formation and IA rupture have different risk factors and underlying pathophysiological mechanisms (9,13).

To explore the risk factors for IA rupture in northern China, we used a case-control design. This study analyzed the gender, age, medical history of patients with ruptured and unruptured IAs (UIAs), and the location of IAs to explore the risk factors of IA rupture, which will provide the theoretical basis for IA rupture. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-820/rc).

Methods

Patient selection

Our study included the patients who were diagnosed as SAH or UIAs in the Department of Neurosurgery at the Second Hospital of Hebei Medical University from 2014 to 2019. They were firstly examined with computed tomography/magnetic resonance imaging (CT/MRI) for such conditions as unconsciousness, epileptic seizure, headache, and cerebral infarction, followed by a physical examination. Patients with SAH resulting from injuries were excluded. The remaining 1,219 patients, including 618 with ruptured IAs and 601 with UIAs, were further diagnosed by digital subtraction angiography (DSA). We further excluded those with vascular dissection and incomplete data. Finally, 1,214 patients including 616 with ruptured IAs and 598 with UIAs were retained for a case-control study (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (No. 2020-R135) and the requirement for individual consent for this retrospective analysis was waived.

Data collection

We collected information about demographics (age, gender), medical history (hypertension, diabetes, heart disease, immune system disorders, metabolic disease, and cerebral infarction), and the characteristics of IAs (location, number). According to the number of IAs, IAs were dichotomized into single IAs (n=1) and multiple IAs (n≥2). Multiple IAs in an individual patient were analyzed separately. When any IA was ruptured, the individual would be categorized into the ruptured group, otherwise they would be categorized into the unruptured group.

Definition of parameters

Internal carotid artery (ICA) aneurysm was defined as an aneurysm in the cavernous segment of the ICA and onwards. The ICA, anterior cerebral artery (ACA), anterior communicating artery (AcoA), posterior communicating artery (PcoA), and posterior cerebral artery (PCA) comprise

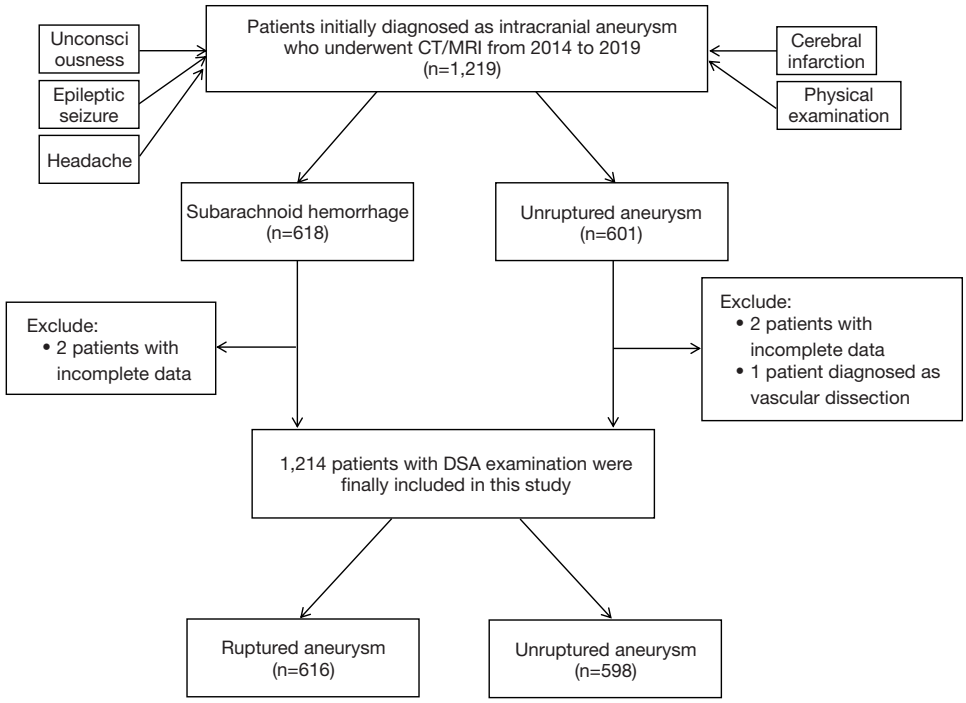

Figure 1 The flow diagram of the participant selection process. CT, computed tomography; MRI, magnetic resonance imaging; DSA, digital subtraction angiography.

the primary collateral arteries of the circle of Willis. We referred to the secondary collaterals (14) except the middle cerebral artery (MCA),vertebral artery (VA), and basilar artery (BA) as branch arteries. The branch arteries we studied were divided into anterior circulation branches (Branch A) (including the ophthalmic artery, anterior choroidal artery, and pericallosal artery) and posterior circulation branches (Branch P) (including the posterior inferior cerebellar artery, superior cerebellar artery, anterior inferior cerebellar artery, thalamoperforating artery, and posterior choroidal artery).

Statistical analysis

Normally distributed quantitative data were presented as mean ± standard deviation, and the independent sample *t*-test was for intergroup comparison. Categorical variables were presented as percentages (%), and the chi-square test was used for intergroup comparison (*Table 1*). Subsequently, in order to identify independent risk factors for rupture, a multivariable logistic regression analysis was performed with the variables chosen based on the univariable analysis. All the variables were evaluated as possible risk factors, with their odds ratios (ORs) and 95% confidence intervals (CIs) presented in *Table 2*. A 2-tailed P<0.05 was considered statistically significant. All the statistical analyses were performed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of participants and univariable analysis

As shown in the *Table 1*, the mean age (57.28±9.63 *vs.* 57.47±12.00, P=0.769), female proportion (63.5% *vs.* 67.0%, P=0.200), and proportion of multiple aneurysms (15.9% *vs.* 19.0%, P=0.154) showed no significant differences between the unruptured group and the ruptured group. As for medical history, prior hypertension, diabetes, heart disease, immune system disorders, and metabolic disease showed no difference between the two groups (P=0.068, P=0.716, P=0.190, P=0.190, and P=0.352, respectively). Interestingly, prior cerebral infarction showed significant differences between the two groups (P<0.001). IAs located in the ICA, AcoA, PcoA, Branch A, VA, and Branch P showed significant differences (P<0.05), whereas IAs located in

Table 1 Results from the univariable analysis of influential factors for IA rupture

Factors	Unruptured group (n=598)	Ruptured group (n=616)	χ^2	P value
Age (years)	57.28±9.63	57.47±12.00	0.293	0.769
Gender			1.641	0.200
Male	218 (36.5)	203 (33.0)		
Female	380 (63.5)	413 (67.0)		
Single/multiple			2.033	0.154
Single	503 (84.1)	499 (81.0)		
Multiple	95 (15.9)	117 (19.0)		
Hypertension			3.327	0.068
Yes	354 (59.2)	396 (64.3)		
No	244 (40.8)	220 (35.7)		
Diabetes			0.132	0.716
Yes	60 (10.0)	58 (9.4)		
No	538 (90.0)	558 (90.6)		
Cerebral infarction			14.629	<0.001
Yes	67 (11.2)	32 (5.2)		
No	531 (88.8)	584 (94.8)		
Heart disease			1.720	0.190
Yes	68 (11.4)	56 (9.1)		
No	530 (88.6)	560 (90.9)		
Immune system disorders			1.720	0.190
Yes	1 (0.2)	4 (0.6)		
No	597 (99.8)	612 (99.4)		
Metabolic disease			0.867	0.352
Yes	13 (2.2)	9 (1.5)		
No	585 (97.8)	607 (98.5)		
Denial of illness			0.044	0.834
Yes	157 (26.3)	165 (26.8)		
No	441 (73.7)	451 (73.2)		
ICA			105.447	<0.001
Yes	233 (39.0)	81 (13.1)		
No	365 (61.0)	535 (86.9)		
MCA			0.042	0.838
Yes	60 (10.0)	64 (10.4)		
No	538 (90.0)	552 (89.6)		
ACA			3.686	0.055
Yes	15 (2.5)	28 (4.5)		
No	583 (97.5)	588 (95.5)		

Table 1 *(continued)*

Table 1 *(continued)*

Factors	Unruptured group (n=598)	Ruptured group (n=616)	χ^2	P value
AcoA			42.145	<0.001
Yes	39 (6.5)	117 (19.0)		
No	559 (93.5)	499 (81.0)		
PcoA			47.199	<0.001
Yes	162 (27.1)	284 (46.1)		
No	436 (72.9)	332 (53.9)		
Branch A			5.303	0.021
Yes	7 (1.2)	19 (3.1)		
No	591 (98.8)	597 (96.9)		
VA			5.148	0.023
Yes	37 (6.2)	21 (3.4)		
No	561 (93.8)	595 (96.6)		
BA			0.108	0.743
Yes	54 (9.0)	59 (9.6)		
No	544 (91.0)	557 (90.4)		
PCA			0.756	0.385
Yes	15 (2.5)	11 (1.8)		
No	583 (97.5)	605 (98.2)		
Branch P			5.303	0.021
Yes	7 (1.2)	19 (3.1)		
No	591 (98.8)	597 (96.9)		

Data are presented as number (percentage) or mean ± standard deviation. IA, intracranial aneurysm; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; AcoA, anterior communicating artery; PcoA, posterior communicating artery; Branch A, anterior circulation branches; VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery; Branch P, posterior circulation branches; single, solitary aneurysm; multiple, multiple aneurysms.

Table 2 Results from multivariable logistic regression for IA rupture

Factors	Regression coefficient	SE	Wald values	P value	OR (95% CI)
Cerebral infarction	–0.929	0.239	15.083	<0.001	0.395 (0.247–0.631)
ICA	–0.909	0.165	30.207	<0.001	0.403 (0.292–0.557)
ACA	0.881	0.342	6.636	0.010	2.413 (1.235–4.718)
AcoA	1.374	0.214	41.426	<0.001	3.952 (2.601–6.006)
PcoA	0.869	0.146	35.241	<0.001	2.385 (1.790–3.177)
Branch A	1.251	0.459	7.437	0.006	3.493 (1.422–8.581)

IA, intracranial aneurysm; ICA, internal carotid artery; ACA, anterior cerebral artery; AcoA, anterior communicating artery; PcoA, posterior communicating artery; Branch A, anterior circulation branches; SE, standard error; OR, odds ratio; CI, confidence interval.

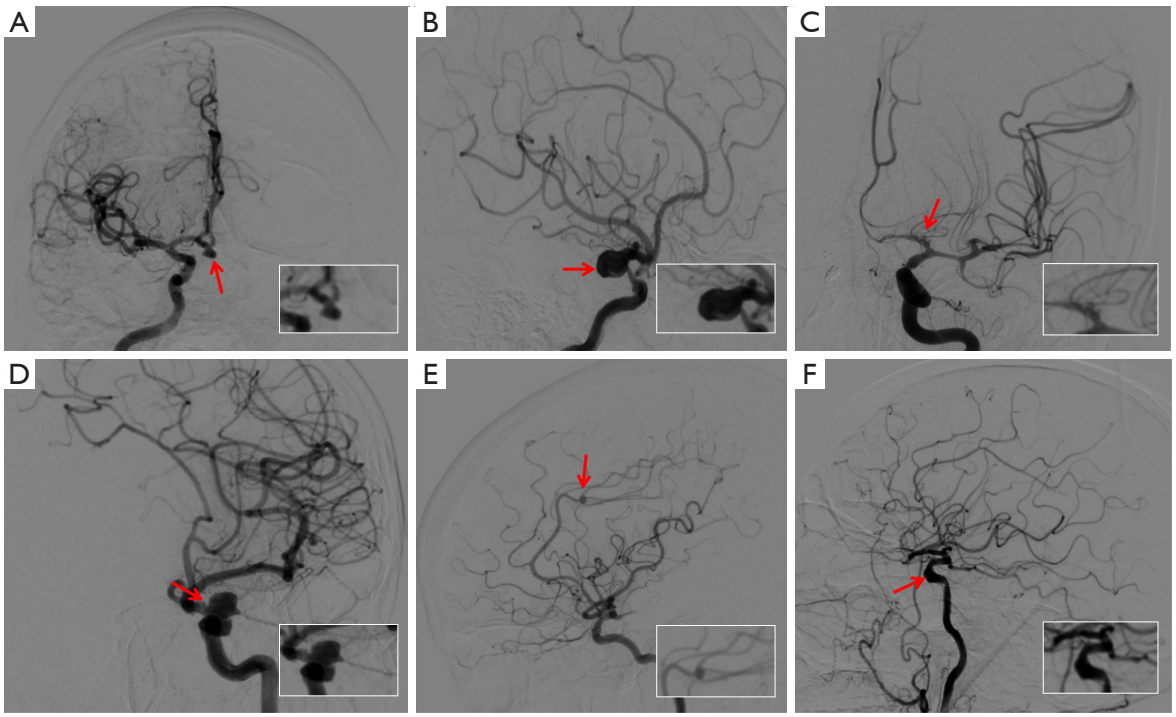

Figure 2 Representative DSA image of high ruptured risk aneurysms (A-E) and lower ruptured risk aneurysms (F) (red arrow). (A) AcoA aneurysm, (B) PcoA aneurysm, (C) ACA aneurysm, (D) ophthalmic artery aneurysm (Branch A), (E) pericallosal artery aneurysm (Branch A), (F) ICA aneurysm. digital subtraction angiography; AcoA, anterior communicating artery aneurysm; PcoA, posterior communicating artery aneurysm; ACA, anterior cerebral artery; ICA, internal carotid artery.

the MCA, ACA, and BA showed no significant differences (P=0.838, P=0.055, and P=0.743, respectively).

Multivariable analysis for influential factors of IA rupture

Using gender, age, single/multiple IAs, hypertension, diabetes, cerebral infarction, heart disease, immune system disorders, metabolic disease, denial of illness, and location of IAs as independent variables, the dependent variable (IA rupture) was estimated in multivariable logistic regression. As displayed in *Table 2*, the results were as follows: (I) cerebral infarction (OR =0.395; 95% CI: 0.247–0.631), ICA (OR =0.403; 95% CI: 0.292–0.557), ACA (OR =2.413; 95% CI: 1.235–4.718), AcoA (OR =3.952; 95% CI: 2.601–6.006), PcoA (OR =2.385; 95% CI: 1.790–3.177), and Branch A (OR =3.493; 95% CI: 1.422–8.581) were independent influential factors for IA rupture (P<0.05). (II) Among them, ACA, AcoA, PcoA, and Branch A were risk factors. Interestingly, prior cerebral infarction reduced the future risk for IA rupture. Also, the results showed IAs located in the ICA were less prone to rupture. Representative images of aneurysms are shown in *Figure 2*. No influence of other factors on IAs rupture was observed.

Discussion

Currently, the risk factors of IA rupture represent a hot research topic. In the present study, we reviewed 1,214 northern Chinese patients with IAs and analyzed their data on demographic characteristics, medical history, and location of IAs. Among these factors, we found that the location of aneurysms was most related to the risk of rupture.

In our study, the mean age of the ruptured group was 57.47±12.00 years, and the mean age of the unruptured group was 57.28±9.63 years, showing no significant intergroup difference in age (P=0.769). Similarly, a British multi-centered study conducted in 2018 (1,729 cases in the ruptured group and 605 cases in the unruptured group) showed the mean age was 53.24 years for ruptured group and 57.03 years for unruptured group (15), with no significant difference in age between the two groups

(P=0.365). This finding also suggested that people aged around 50 years should pay attention to IAs and the prevention of IA rupture (1). This British study also showed no significant difference in gender between the two groups (P=0.242) (15). Consistently, our study found that gender was not an independent risk factor for IA rupture (P=0.200), yet female gender has been reported to significantly increase the relative risk of IA rupture in other studies (16,17).

It is well-established that hypertension is a risk factor for the formation of IAs (18-21). However, a Japanese study conducted in 2010 showed that although hypertension was associated with an elevated risk of aneurysmal SAH, hypertension had no direct association with IAs rupture (22). In addition, antihypertensive medications play an important role in the rupture of IAs. An animal study demonstrated that after the formation of IAs in mice, the risk of IA rupture would not increase when blood pressure was restored to normal levels (23). Clinical research has also shown that the risk of IA rupture would not be elevated after standardized hypertension treatment (15). In our study, 59.2% of the unruptured group had hypertension, which was lower than the proportion of 64.3% in the ruptured group, yet without significant differences (P=0.068), suggesting that hypertension was not a risk factor for IA rupture. However, our study lacked an investigation into blood pressure control in hypertensive patients. A previous study showed that patients with IAs could benefit from regular blood pressure monitoring (24). Studies have shown that with the implementation of community-based hypertension management programs, the majority of Chinese hypertensive patients achieved blood pressure control (25,26). Therefore, blood pressure control may reduce the risk of IA rupture.

Cerebral infarction is the most common cerebrovascular disease. Our study found that prior cerebral infarction could reduce the occurrence of IA rupture in the future (OR =0.395; 95% CI: 0.247–0.631; P<0.001). Aspirin, as a salicylic acid-based drug, is a first-choice drug for patients after cerebral infarction, where long-term use is required. Several studies have indicated that aspirin plays protective roles in the formation, growth, and rupture of IAs (27-30). Aspirin has anti-inflammatory effects. Previous animal and clinical studies have shown that aspirin reduces the risk of rupture by inhibiting COX-2 and regulating the pro-inflammatory environment of the vascular wall of IAs (31). However, a study showed that aspirin did not affect the outcome of patients with ruptured aneurysms (31). In addition, cerebral angiography examinations, such as magnetic resonance angiography (MRA) and computed tomography angiography (CTA), have been routinely used for patients after cerebral infarction, which will greatly increase the detection rate of IAs and prompt patients to take preventive measures for IAs at a higher risk of rupture. This is another explanation for the low risk of IA rupture in patients after cerebral infarction.

Previous studies have indicated that there are several risk factors for IA rupture (8,9,11,32). According to statistics, multiple IAs are present in approximately 30% of patients with IA (1,33). A Japanese prospective clinical study carried out in 12 national centers pointed out that multiple IAs were one of the risk factors for rupture (34). However, a study conducted by Rinaldo *et al.* (12) found that multiple IAs were not a risk factor for rupture. The high risk of rupture reported previously for patients with multiple IAs might reflect the cumulative risk of rupture rather than the risk per IA (4). In this study, the rupture rate of patients with only 1 aneurysm was 49.80%, whereas that of patients with multiple aneurysms was 55.19%. The number of aneurysms was not a factor for rupture in the population of northern China, so we further explored the location of IAs.

The location of IAs may play an important role in the rupture risk of IAs (8,33). IAs commonly occur in the circle of Willis (33). The morphological variations of the ACA and AcoA are large, among which the most common anatomic variation is a maldeveloped A1 segment of the ACA (around 20% in the total population) (35,36). A maldeveloped ACA-A1 not only facilitates the formation of AcoA aneurysms, but also possibly influences the size and shape of ACA aneurysms (37). In addition, as shown in other large prospective studies, AcoA has a relatively high rupture risk due to its relatively high wall shear stress (4,11,38), which serves as a non-invasive biomarker for IA rupture (39). IAs located at the bifurcation is a risk factor for UIA progression (40). In our multivariable logistic regression, IAs located in the ACA (OR =2.413; 95% CI: 1.235–4.718; P=0.01) and AcoA (OR =3.952; 95% CI: 2.601–6.006; P<0.001) had an evidently elevated risk of rupture. PcoA aneurysms commonly arise from the ICA-PcoA junction, which were also a risk factor for rupture. Our study revealed that PcoA aneurysms had a significant risk of rupture (OR =2.385; 95% CI: 1.790–3.177; P<0.001), which was consistent with a majority of previous studies (4,15), despite some studies reporting no significant differences (11). Our study showed that ICA aneurysms (OR =0.403; 95% CI: 0.292–0.557; P<0.001) had the lowest risk of rupture, which was in line with many previous studies

(41,42). The PHASES study pooled the analyses of six prospective cohort studies and found that aneurysms in the ACAs (including the ACA, AcoA, and pericallosal artery), PcoA, and posterior circulation branches (Branch P) had the highest risk of rupture, whereas ICA aneurysms had the lowest risk of rupture (8). A study on the hemodynamics of aneurysms at different locations pointed out that ICA aneurysms had lower size ratios, less low wall shear stress areas, and lower pressure loss coefficients, which might be subjected to less adverse hemodynamic environments (38). Another study confirmed that ICA aneurysms had significantly lower pressure loss coefficients, which were associated with a lower risk of rupture (43).

There are scarce studies on aneurysms in branch arteries. As a branch of ACAs, the pericallosal artery has a higher risk of rupture (8). Our results also revealed that aneurysms in Branch A had an evidently elevated risk of rupture (OR =3.493; 95% CI: 1.422–8.581; P=0.006). Due to the small sample size, we did not conduct further analysis by dividing Branch A into different categories. Our findings provide a new direction for future studies on the risk of IA rupture.

Study limitations

Our study has some limitations. First, we lacked the data about the size and shape of IAs. Our finding that the location of aneurysms was most related to the risk of rupture in the population from northern China might be biased due to a lack of non-location variables in our multivariable model. Second, our study lacked an investigation into blood pressure control in hypertensive patients, which might be the hidden confounder for our result on the association between hypertension and IA rupture. Third, all the cases were diagnosed by DSA. Although DSA has the highest accuracy, many patients with unruptured aneurysms diagnosed by MRA or CTA were not included. Last, our study was conducted in a population from northern China, which was a single-centered study with a limited sample size.

Conclusions

Our study found that prior cerebral infarction and IAs located in the ICA were associated with IA rupture, whereas IAs located in the ACA, AcoA, PcoA, and Branch A were associated with a higher risk of IA rupture in the population from northern China. Effective measures targeted at specific risk factors of IA rupture should be taken in its prevention.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-820/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-820/coif). L.Z. reports that this work was supported by the S&T Program of Hebei, China (No. 20377702D). Y.W. reports that this work was supported by the Key Project of Medical Science Research of Hebei Province, China (No. 20230063). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (No. 2020-R135) and individual consent for this retrospective analysis was waived.

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