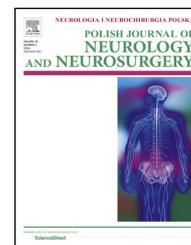


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## Original research article

# Impact of hypertension and smoking on the rupture of intracranial aneurysms and their joint effect



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## ABSTRACT

**Background:** In general population, the prevalence of intracranial aneurysm reaches as high as three percent. The goal of the study was to analyze retrospectively the independent risk factors for the rupture of intracranial aneurysms and their joint effect.

**Methods:** The records and angiographies of continuous 519 intracranial aneurysm patients treated at our center between February 2013 and July 2014 were retrospectively analyzed. Ruptured group and unruptured group were included in the study according to their clinical and imaging information. Univariate analysis and multivariate logistic regression analysis was used to identified independent risk factors for the rupture of intracranial aneurysms. We assessed the joint effect of independent risk factors for the rupture of intracranial aneurysms with an additional logistic regression analysis.

**Results:** The results of multivariate analysis show that hypertension (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.05–2.18) and smoking (odds ratio [OR], 1.57; 95% confidence interval [CI], 1.06–2.33) were independent risk factors for rupture of intracranial aneurysms. The joint risk of hypertension and smoking was higher (OR, 2.28; 95% CI, 1.29–4.02) than the risks of hypertension (OR, 1.74; 95% CI, 1.11–2.72) and smoking (OR, 1.86; 95% CI, 1.05–3.29) independently.

**Conclusions:** Hypertension and smoking increase of the rupture risk of intracranial aneurysms. And the joint risk of hypertension and smoking was higher than the risks of hypertension and smoking independently.

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## 1. Introduction

In general population, the prevalence of intracranial aneurysm reaches as high as 3% [1].

Although only a minority of aneurysms rupture, but the morbidity and mortality causing case death rates caused by aneurysmal rupture are between 25 and 50% [2]. So reducing the incidence of aneurysmal subarachnoid hemorrhage is very important for patients who harbor an unruptured intracranial aneurysm [3].

Systemic hypertension and smoking have long been considered independent risk factors of aneurysmal rupture [4–7]. Studies on other modifiable risk factors, such as age, gender, heart disease, hypercholesterolemia, diabetes mellitus, family history of stroke other than subarachnoid hemorrhage and excessive alcohol use as independent risk factors, are limited or sometimes conflicting [8–12]. And study on the joint effect of the risk factors for intracranial aneurysm is few [13].

The goal of the study was to analyze retrospectively the independent risk factors for the rupture of intracranial aneurysms from lifestyle and medical history data in China and their joint effect.

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## 2. Methods

### 2.1. Patient selection

A retrospective of 17 months continuous clinical database from February 2013 to July 2014 in our institution was reviewed for all patients with aneurysms. We collected the clinical records and imaging data in details, including magnetic resonance angiography, CT angiography and digital subtraction angiography (DSA). Patients with complete clinical and imaging information were enrolled into our study. All included patients in this study had available imaging with conventional DSA, including bilateral external carotid arteries, bilateral internal carotid arteries, and bilateral vertebral arteries to assess the arterial supply and lesion location.

### 2.2. Data collection

The clinical and imaging information of all included patients were complete. We collected the information of age, gender, hypertension, heart disease, hypercholesterolemia, diabetes mellitus, family history of stroke other than subarachnoid hemorrhage, smoking and excessive alcohol use. Smoking status was stratified into 3 groups according to each patient's medical history: (1) never a smoker, (2) current smoker (smoked at the time of treatment), and (3) former smoker (quit smoking before treatment) [14]. And smoking was defined as current smoker and former smoker [13]. Excessive alcohol use was defined as alcohol consumption  $\geq 18$  U (i.e.,  $\geq 150$  g) per week [15]. All patients were asked whether they had been diagnosed with having hypertension, heart disease, hypercholesterolemia, diabetes mellitus before discovery of the intracranial aneurysm. History of heart disease was defined those persons who had a angina pectoris, myocardial

infarction, coronary artery bypass grafting, and percutaneous transluminal coronary arterioplasty [13]. The study population was 18 years old and above.

Cases of SAH (subarachnoid hemorrhage) due to moyamoya, trauma, arteriovenous malformation, dural arteriovenous fistula, pregnancy-induced hypertension, connective tissue disease, arterial dissection, or unknown etiology were excluded. Cases without complete clinical and imaging information were also excluded from this study.

### 2.3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) was used to analyze the association between clinical characteristics and rupture risk. Continuous variables were expressed in the form of mean  $\pm$  standard deviation, and categorical variables were used Pearson's chi-squared test. To identify independent risk factors for rupture from aneurysms, univariate analyses and multivariate logistic regression analysis (forward stepwise conditional) were performed for clinical characteristics parameters. The joint effect of independent risk factors for the rupture of intracranial aneurysms was assessed with an additional logistic regression analysis. A *p*-value  $< 0.05$  was regarded as statistically significant, and the odds ratios (OR) with 95% confidence intervals (CI) were also calculated.

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## 3. Results

### 3.1. Study population

A continuous database including 519 patients with 589 aneurysms. Eighty-three (14.1%) aneurysms on the anterior cerebral artery (ACA), 361(61.3%) aneurysms on the internal carotid artery, 34(5.8%) aneurysms on the middle cerebral artery (MCA) and 111(18.8%) aneurysms on the vertebrobasilar artery (VBA). One hundred and ninety-six patients were male, and three hundred and twenty-three patients were female. Their mean age was  $54.1 \pm 11.6$  years. These 519 patients included 341 patients with unruptured aneurysms and 178 patients with ruptured aneurysms. Patients were divided into ruptured group and unruptured group according to their clinical and imaging information. The baseline demographic data and risk factor data of patients are summarized in Table 1.

### 3.2. Univariate analysis and multivariate logistic regression analysis of risk factors for rupture of intracranial aneurysms in patients

Univariate analysis showed that hypertension (odds ratio [OR], 1.50; 95% confidence interval [CI], 1.04–2.16) and smoking (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.05–2.31) were statistically significant associated with intracranial aneurysm rupture. Further multivariate analysis indicated that hypertension (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.05–2.18) and smoking (odds ratio [OR], 1.57; 95% confidence interval [CI], 1.06–2.33) were still significant factors in predicting rupture from aneurysms (Table 2). In addition, the odds ratio value were 1.51 and 1.57 in logistic regression analyses,

**Table 1 – Baseline characteristics of rupture and unrupture groups.**

	Rupture	Unrupture	Total
Gender			
Male	75	121	196
Female	103	220	323
Age	54.2 ± 12.1	54.1 ± 11.3	519
Hypertension			
No	76	180	256
Yes	102	161	263
Heart disease			
No	166	316	482
Yes	12	25	37
Hypercholesterolemia			
No	161	301	462
Yes	17	40	57
Diabetes mellitus			
No	159	315	474
Yes	19	26	45
Stroke <sup>a</sup>			
No	158	300	458
Yes	20	41	61
Smoking			
No	116	254	370
Yes	62	87	149
Alcohol use			
No	121	246	367
Yes	57	95	152

<sup>a</sup> Including hemorrhagic and ischemic stroke, but not including subarachnoid hemorrhage.

indicating hypertension and smoking were significant predictors of aneurysmal rupture.

### 3.3. The joint risk of hypertension and smoking for rupture of intracranial aneurysms in patients

The joint risk of smoking and hypertension (OR, 2.28; 95% CI, 1.29–4.02) was higher than the individual risks for hypertension (OR, 1.74; 95% CI, 1.11–2.72) and smoking (OR, 1.86; 95% CI,

**Table 2 – Risk factors for unruptured intracranial aneurysms.**

	Univariable analysis (n) OR (95% CI)	Multivariable analysis (n) OR (95% CI)
Gender	0.76 (0.52–1.095)	–
Age	0.937 <sup>b</sup>	–
Hypertension	1.50 (1.04–2.16)	1.51 (1.05–2.18)
Heart disease	0.91 (0.48–1.87)	–
Hypercholesterolemia	0.80 (0.44–1.45)	–
Diabetes mellitus	1.45 (0.78–2.70)	–
Stroke <sup>a</sup>	0.93 (0.53–1.64)	–
Smoking	1.56 (1.05–2.31)	1.57 (1.06–2.33)
Alcohol use	1.22 (0.82–1.81)	–

CI, confidence interval; OR, odds ratio.

<sup>a</sup> Including hemorrhagic and ischemic stroke, but not including subarachnoid hemorrhage; –, not statistically significant in multivariate analysis

<sup>b</sup> Age ( $P = 0.937$ ).

**Table 3 – Interaction between hypertension and smoking for the risk of aneurysm.**

	Rupture	Unrupture	Total	OR (95% CI)
No hypertension, no smoking	47	135	182	Ref
Hypertension, no smoking	69	119	188	1.74 (1.11–2.72)
Smoking, no hypertension	29	45	74	1.86 (1.05–3.29)
Hypertension and smoking	42	33	75	2.28 (1.29–4.02)

CI, confidence interval; OR, odds ratio.

1.05–3.29) independently (Table 3). And this combined effect can be clearly seen in the figure, the risk of smoking and hypertension group was significantly higher than other groups (Fig. 1).

## 4. Discussion

In this study, we found that hypertension and smoking increase of the rupture risk of intracranial aneurysms. And the joint risk of hypertension and smoking was higher than the risks of hypertension and smoking independently.

Many previous studies had reported that hypertension can increase the risk for aneurysmal rupture [15–19]. The aneurysmal wall may be weakened by directly increasing mechanical stresses and activation of the local renin-angiotensin system since the long-term effects of hypertension, and systemic hypertension can cause vascular inflammation and remodeling which may contribute to aneurysmal rupture [20]. Previous studies reported that aneurysmal rupture is associated with certain polymorphisms in the genes related to the renin-angiotensin system [21–23]. Tada et al. [4] made an animal experiment of intracranial aneurysms to evaluate the role of systemic hypertension and of the renin-angiotensin system on aneurysmal rupture. Tada et al. found that controlled (<140/90 mmHg/normalization, after regularly taking antihypertensive drugs) hypertension after aneurysm formation could prevent aneurysmal rupture in mice and the inhibition of the local renin-angiotensin system independent from the reduction of blood pressure can prevent aneurysmal rupture [4]. Robert [24] found that TNF- $\alpha$  is very important in the formation and rupture of aneurysms. And the hemodynamic stress associated with hypertension in rats in vivo can increase the expression of TNF- $\alpha$ . Therefore, systemic hypertension may directly or indirectly contribute to aneurysmal rupture. In our clinical study, we also confirmed that hypertension can increase of the rupture risk of intracranial aneurysms and the odds ratio value was 1.51.

Many studies also reported that smoking is an independent risk factor for aneurysmal rupture [11–13,25,26]. In our study, univariate analysis and multivariate logistic regression analysis also showed that smoking is a significant predictor of aneurysmal rupture, the odds ratio value of smoking was 1.57 (95% confidence interval [CI], 1.06–2.33). The vascular homeostasis and structural integrity will be affected since the long-term effects of smoking, and a deficiency of alpha

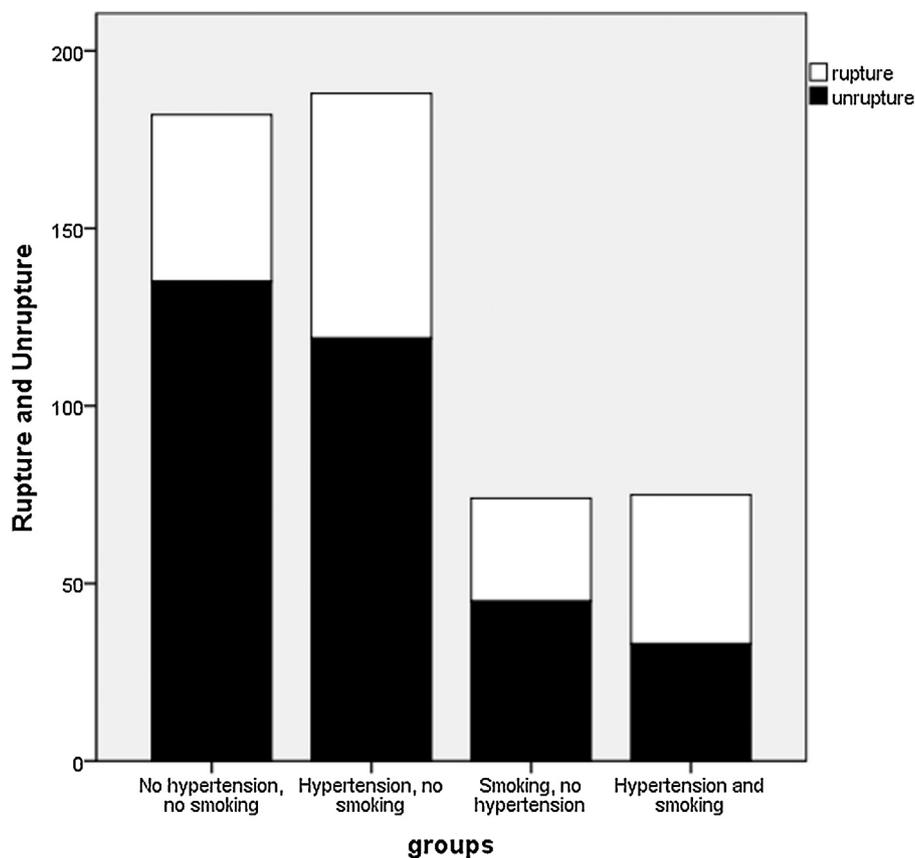


Fig. 1 – Ruptured and unruptured cases by hypertension and smoking group.

1-antitrypsin or one of the other protease inhibitors could result in degradation of the arterial wall through an imbalance between proteolytic enzymes and their inhibitors, thereby predisposing the arterial wall to dissection or aneurysm formation [27–29].

Monique [13] reported that hypertension and current smoking increase the rupture risk of unruptured intracranial aneurysm and the joint risk was higher than the sum of the separate risks. Another study reported that patients with a history of hypertension and smoking have a lower threshold of aneurysm rupture than patients without these risk factors [30]. In our study, we did not find that smoking and hypertension had combined a higher risk than the sum of the separate risks, but the joint risk of hypertension and smoking was higher than the risks of hypertension and smoking independently.

This study has some limitations. The sample size in this study is still small, relative ratio may be a better measure if the sample size could be further expanded. Our study only represents experience at a single institution which possibly introduce a demographic bias. In addition, as lack of statistical power, it is possible that other significance variables were lack for our study.

In conclusion, hypertension and smoking increase of the rupture risk of intracranial aneurysms. And the joint risk of hypertension and smoking was higher than the risks of hypertension and smoking independently. Well-controlled

hypertension and smoking cessation is very important for patients with an unruptured intracranial aneurysm.

#### Conflict of interest

None declared.

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#### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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