



## Original Research Article

## Smoking index- A measure to quantify cumulative smoking exposure

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## ABSTRACT

**Background and Purpose:** We aimed to investigate the effect of smoking on the risk of intracranial aneurysm (IA) rupture (IAR), specifically relationship between the number of cigarettes smoked per day (CPD) or smoking index and the risk of IAR.

**Materials and Methods:** We performed a single-center case-control study of consecutive patients evaluated or treated for IA at our institution from June 2017 to July 2018. Cases were patients with a ruptured IA. Two age- and sex-matched controls with an unruptured IA were included per case. Conditional logistic regression models were used to assess the relationship between both the CPD and smoking index (CPD × years of smoking) and IAR.

**Results:** The study population included 300 cases of IAR and 300 controls. The higher IAR risk was associated with cigarette smoking. Our subgroup analysis of smokers revealed a significant association between IAR risk and current smoking (OR, 2.8; 95% CI, 1.2–6.3; P=0.012), current heavy smoking (CPD ≥ 20) (OR, 3.9; 95% CI, 1.4–11.0; P=0.007), and a smoking index ≥ 800 (OR, 11.4; 95% CI, 2.3–24.5; P=0.003).

**Conclusion:** A dose-response relationship has been noted for intensity and duration of smoking consumption and increased risk of IAR. As smoking is modifiable, this finding is important to managing patients with IAs to quit or reduce smoking prior to life-threatening subarachnoid hemorrhage.

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## 1. Introduction

Nearly 3% of the adult population was found to have an unruptured intracranial aneurysm (IA).<sup>1</sup> With the increasing use of cranial imaging, more incidental IAs is being detected in clinical practice. Although the annual risk of rupture of asymptomatic IA is relatively low, subarachnoid hemorrhage (SAH) caused by IA rupture associated with high rates of morbidity and mortality.<sup>2</sup> Prevention is better than cure. Hence, to prevent SAH via modifiable risk factors identification and management, rather than surgical

clipping and intravascular intervention, is of great clinical and social value. Smoking is the most important established risk factor for IA rupture,<sup>3–6</sup> and up to 80% of patients who sustain an aneurysmal SAH have a history of smoking, and 50–60% are current smokers.<sup>7,8</sup> A Finnish register-based study reported that the incidence of SAH was decreasing and this trend may be associated with changes in smoking rates, suggesting the possible benefits of smoking cessation.<sup>9</sup> However, the predictors of adverse outcome after smoking exposure have not been clearly identified, and most studies have simply stratified subjects based on the presence or absence of a history of cigarette smoking.<sup>7,8</sup> Using quantitative indicators within the smoking history,

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such as the number of cigarettes smoked per day (CPD) and smoking index (CPD  $\times$  years of tobacco use),<sup>10</sup> may lead to a more detailed understanding of the mechanisms by which smoking contributes to aneurysm formation and rupture and helps to develop strategies to reduce the risk of rupture. We, therefore, devised a case–control study to investigate the effect of smoking on the risk of IA rupture, specifically the relationship between the CPD and smoking index and rupture risk.

### 1.1. Patient selection

We performed a single-center case–control study of consecutive patients evaluated or treated for IA at our institution from June 2017 to July 2018. Cases were defined as patients with SAH secondary to a ruptured IA and controls as patients harboring a UIA. Two controls were randomly selected from the patients admitted with a diagnosis of UIA and matched to each case based on age ( $\pm 5$  years) and sex. All enrolled patients were examined using three-dimensional rotational angiography. For all cases, SAH was diagnosed using computed tomography (CT).

### 1.2. Our exclusion criteria included

(1) dissecting, fusiform, traumatic, mycotic, or partially thrombosed aneurysms; (2) the patients with nonaneurysmal SAH examined by digital subtraction angiography (DSA), or the location of ruptured aneurysm could not be identified among multiple IAs by CT and DSA; (3) aneurysms without clear and readable three-dimensional rotational angiography that allowed an evaluation of lesion geometry and morphology; (4) aneurysms associated with cerebral arteriovenous malformation, arteriovenous fistula, or moyamoya disease. The study was approved by the review committee of our hospital, and informed consent was obtained from all the subjects.

### 1.3. Data collection and definitions

Information on smoking was obtained from the medical history recorded by the treating physicians during interviews of patients or family members. If the patient's information was incomplete, we obtained information using a telephone survey. All patients were asked "Have you ever smoked?" and if the answer was yes, "For how many years in total have you smoked?", "how long ago did you quit smoking?", and "Do you currently smoke?" Individuals who were current smokers or former smokers were asked to report the mean number of cigarettes, pipes, and cigars smoked per day. Nonsmokers affirmed that they had never smoked or smoked <100 cigarettes (lifetime). Patients who smoked at the time of treatment or smoked  $\geq 100$  cigarettes during the past year were considered current smokers. Patients who had smoked

$\geq 100$  cigarettes but had not smoked during the past year were considered former smokers.<sup>10</sup> The smoking index is a unit for measuring cigarettes consumption over a long period and was calculated using the following formula: smoking index = CPD  $\times$  years of tobacco use. Smoking index categories were nonsmoker, <400, 400–799, and  $\geq 800$ .<sup>11</sup> The CPD was estimated for current and former smokers. We defined heavy smoking as  $\geq 20$  CPD and mild smoking as <20 CPD.<sup>12</sup> We investigated other potential risk factors for aneurysmal rupture. Social-demographic characteristics included age, sex, and educational level, and clinical characteristics included body mass index (BMI), comorbidities, coronary artery procedures, alcohol use (current or previous intake >5 drinks per day), and family history of IA. A BMI  $\geq 25$  kg/m<sup>2</sup> was defined as overweight.<sup>13</sup> All morphological parameters were obtained by three-dimensional rotational angiography and evaluated by two experienced neurosurgeons.

### 1.4. Statistical analyses

All statistical analyses were performed using SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, New York, USA). Continuous variables were analyzed using the Mann–Whitney U test or Student's t-test and are presented as mean  $\pm$  SD or medians (interquartile ranges). Categorical variables were analyzed using Fisher's exact test or the Pearson chi-square test and are presented as frequencies (percentages). Associations between smoking history and intracranial aneurysm rupture (IAR) were assessed using Fisher's exact test or the linear-by-linear association test. Because our study was performed on a matched sample, the Cochran–Mantel–Haenszel test was also performed. As predetermined, variables with a  $P < 0.20$  in the univariate logistic regression analysis were evaluated in our multivariate analysis. Because the sample was matched, we used conditional logistic regression to calculate univariate and multivariate odds ratios (ORs) with 95% confidence intervals (CI). A  $P$ -value <0.05 was regarded as statistically significant.

## 2. Results

A total of 1000 patients with IAs were evaluated or treated at our institution during the study period. After applying our exclusion criteria, 300 cases of IAR and 680 cases of unruptured IAs were included. However, 20 cases of ruptured IAs failed to find their matched controls. Consequently, our study population was composed of 127 cases of IAR and 254 matched controls with UIAs

The frequency and odds of risk factors in IAR cases compared to controls. The following covariates met our previously determined level of significance and entered the stepwise forward selection for the conditional logistic model: smoking status (nonsmoking, former smoking, and

current smoking;  $P$  with significant  $p$  value),  $BMI \geq 25$  ( $P > 0.05$ ), alcohol use ( $P < 0.05$ ), history of hyperlipidemia ( $P < 0.05$ ), diabetes mellitus ( $P < 0.05$ ), aneurysm size ( $P < 0.05$ ).

Cases and controls also showed significant differences in frequency and risk of IAR based on smoking status determined by CPD [nonsmoker, former smoker, mild current smoking ( $CPD < 20$ ), and heavy current smoking ( $CPD \geq 20$ );  $P < 0.05$ ] and smoking index (nonsmoker, former smoker, and current smoker with smoking indexes of  $< 400$ ,  $400-799$ , and  $\geq 800$ , respectively;  $P < 0.05$ ).

### 3. Discussion

In this case–control study, we demonstrated that a  $CPD \geq 20$  and a high smoking index were strong risk factors for IAR. Furthermore, compared with former smokers who had quit at least 1 year before evaluation, current smokers were more predisposed to IAR, suggesting the importance of smoking cessation in patients with an IA.

Similarly, in their case–control study of 250 patients with an aneurysmal SAH and 206 patients with a UIA, Monique et al. found that current smoking increased the risk of IAR.<sup>7</sup> One possible explanation is that most smoking-induced changes are reversible after quitting, although previous studies suggested that former smokers demonstrate an ongoing low-grade inflammatory response that persists long after smoking cessation.<sup>14</sup> Cigarette smoke is an aerosol containing thousands of chemicals, including nicotine, carbon monoxide, and oxidant compounds,<sup>14</sup> and chronic exposure induces multiple pathological effects in the vascular endothelium and facilitates inflammation. This process consistently weakens the UIA wall making it more vulnerable to trigger factors and eventually leads to rupture. Aneurysm growth has also been shown to be increased by current smoking supporting the concept that smoking increases SAH particularly by increasing aneurysm size and possibility of rupture.<sup>15,16</sup> Although the CPD was a strong and independent risk factor for UIAs in our study, it should be noted that this straightforward index of cumulative exposure does not take the duration of smoking into account. Therefore, we used the smoking index to investigate whether the increased risk of IAR due to smoking is modifiable. This index can make strong assumptions regarding the equivalence of the roles of intensity and duration.<sup>17</sup> We found a significant association between the smoking index and the risk of IAR. Our results are congruent with the basic research findings that the effects of cigarette smoke on endothelial cells are only functional initially, while the endothelial-cell layer exhibits physical damage and can even be completely destroyed by chronic exposure of cigarette smoke (increase of smoking index).<sup>18</sup> Moreover, increasing degrees of smoking may be more permissive to accelerate morphological changes of aneurysms.<sup>19</sup> These changes, in turn, may increase the

eventual rupture risk of the aneurysm. We confirmed this association using a conditional logistic regression model. However, the association between a smoking index of  $400-799$  and the risk of IAR did not reach statistical significance in our study. This result may be due to our retrospective study design and limited sample size.

In our study, 73.2% of ruptured aneurysms were in a bifurcation location, and this location was an independent risk factor that raised the risk of IAR by a factor of 10.972. This finding is consistent with previous reports.<sup>17</sup> The arterial wall is consistently weakened, where it bifurcates because this area correlates with increased hemodynamic stress and higher blood flow. Thus, IAs in bifurcation locations have a higher risk of rupture than those in other locations.<sup>20</sup> What is more, we analyzed the risk for IAR of bifurcation location among smokers (current smoking/former smoker) and nonsmokers, respectively. Our results showed that the bifurcation risk increased for smokers and nonsmokers.

The risk of IAR in female smokers might be greater than the rupture risk in male smokers. This hypothesis is supported by several studies reporting a dramatic sex-based difference in risk at a given level of cigarette consumption.<sup>20,21</sup> In their community-based case–control analysis, Bonita et al. demonstrated that cigarette smokers had a significantly increased risk of SAH compared with nonsmokers with relative risks of 3.0 and 4.7 for men and women, respectively.<sup>20</sup> Age is an important independent risk factor for acute aneurysm rupture,<sup>21,22</sup> and one of the most important factors affecting cigarette consumption duration. We matched cases based on year of birth (age  $\pm 5$  years) and sex to avoid introducing variability.

Our study showed that hyperlipidemia independently decreased the risk of IAR. Recently, several studies reported similar results.<sup>5,17</sup> Interestingly, a recent study reported an association between the administration of statins and reduced UIA formation in rats.<sup>17</sup> It may be that hypercholesterolemic patients treated with statins gain a similar protective benefit. BMI also independently decreased the risk of IAR, a finding similar to that reported by Monique et al.<sup>5</sup> In their study of 305 patients with SAH, Hughes et al. reported that BMI was inversely related to short- and long-term mortality.<sup>23</sup> However, few other studies demonstrating an association between BMI and aneurysm rupture are available. We also found that diabetes mellitus was associated with a decreased risk of IAR. It has been hypothesized that many patients had presented for evaluation of their diabetes mellitus, allowing some IAs to be diagnosed before they ruptured or altering lifestyle factors and continuing medical care to reduce the risk of SAH. However, the biological foundation of this inverse correlation needs further investigation.

#### 4. Conclusion

Patients with IA who smoked had a greater risk of aneurysm rupture compared with those who were nonsmokers or former smokers. The strength of the association between current smoking and the risk of aneurysmal rupture was directly related to the smoking index and CPD. Information from the current study may be beneficial to increase the potential for patients harboring IAs to quit or reduce smoking prior to life-threatening SAH.

#### 5. Source of Funding

None.

#### 6. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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