



# Risk factors predicting a higher grade of subarachnoid haemorrhage in small ruptured intracranial aneurysm (< 5 mm)

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## ABSTRACT

**Aim.** To identify the risk factors for clinical and radiographic grades of subarachnoid haemorrhage (SAH) in small (< 5 mm) intracranial aneurysms (SIAs).

**Material and methods.** We retrospectively analysed patients with SIAs treated in our centre between February 2009 and June 2018. The clinical status was graded using the Hunt and Hess (H&H) score and the radiological severity of SAH was graded by Fisher grades (FG). The risk factors were determined using multivariate logistic regression analysis.

**Results.** A total of 160 patients with ruptured SIAs (< 5 mm) were included. In univariate analysis, smoking ( $P = 0.007$ ), alcohol use ( $P = 0.048$ ), aspirin use ( $P = 0.001$ ), and higher size ratio (SR) ( $P = 0.001$ ) were significantly associated with a higher H&H grade (3–5) in SIAs; and smoking ( $P = 0.019$ ), aspirin use ( $P = 0.031$ ), inflow angle < 90 degrees ( $P = 0.011$ ), and aneurysm size ( $P = 0.039$ ) were significantly associated with a higher FG score (3–4). In the adjusted multivariate analysis, previous SAH (OR, 12.245, 95% CI, 2.261–66.334,  $P = 0.004$ ), aspirin use (OR, 4.677, 95% CI, 1.392–15.718,  $P = 0.013$ ), alcohol use (OR, 3.392, 95% CI, 1.146–10.045,  $P = 0.027$ ), inflow angle < 90 (OR, 3.881, 95% CI, 1.273–11.831,  $P = 0.017$ ), and higher SR (OR, 6.611, 95% CI, 2.235–19.560,  $P = 0.001$ ) were independent risk factors for a higher H&H grade in ruptured SIAs; smoking (OR, 2.157, 95% CI, 1.061–4.384,  $P = 0.034$ ), and inflow angle < 90 degrees (OR, 2.603, 95% CI, 1.324–5.115,  $P = 0.006$ ) were independent risk factors for a higher FG (3–4).

**Conclusions.** This study revealed that inflow angle < 90 degrees and size ratio, but not absolute size, may highly predict poorer grade of SAH in SRA. Aspirin use, previous SAH, and alcohol use were significantly associated with a higher H&H grade in ruptured SIAs, and smoking was a significant predictor of poorer FG.

**Key words:** intracranial aneurysm, small, rupture, aspirin use, Hunt and Hess score, Fisher grade

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## Introduction

With a 30-day mortality rate of 40%, the most serious damage caused by intracranial aneurysms (IAs) is subarachnoid haemorrhage (SAH) [1–3]. The rupture risk of IAs has been known to increase with increasing aneurysm size. However, some authors have found that the incidence of SAH caused by small aneurysms was increased [4–7], and have clearly demonstrated that approximately 13–50% of ruptured IAs (RIAs) were small (< 5 mm) [8, 9]. As with large aneurysms, the most widely used scales for grading the disease severity of SAH in small (< 5 mm) intracranial aneurysms (SIAs) are the Hunt and Hess (H&H) and the Fisher grades (FG). Many articles have indicated that small aneurysms have different morphological characteristics; however, whether these characteristics are related to the disease severity of SAH is still unclear.

There is a plethora of available literature reporting metabolic indicators as potential markers of the disease severity of an SAH [10, 11]. Although different morphologic parameters such as aspect ratio (AR), size ratio (SR), and inflow angle have been believed to contribute significantly to determining the risk of small aneurysm rupture [9, 12–14], the impact of these morphologic features on the severity of SAH caused by an SRA still remains unexplored.

In addition, antiplatelet agents (aspirin in particular) have emerged as possible options for noninvasive treatment of IAs to decrease the incidence of aneurysmal SAH. On the other hand, according to a meta-analysis of seven studies, aspirin use may be significantly associated with an increased risk of aneurysm rupture [15]. However, the association between aspirin use and the clinical and radiographic grades of SAH caused by SIAs remains unclear.

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For small aneurysms (< 5 mm) that are often considered to be at a low risk of rupture, conservative treatment is generally recommended clinically [8, 9, 12], so small aneurysms are the most likely type of aneurysm to receive conservative observations and protective treatments such as taking aspirin. Therefore, it is important to investigate the risk factors affecting the severity of SAH caused by small aneurysms.

In this study, we aimed to investigate the effects of morphologic parameters and history of aspirin use on clinical and radiographic grades of SAH caused by SIAs.

## Material and methods

A total of 160 patients (84 women and 76 men) with ruptured small IAs (SIA) (< 5 mm) who were diagnosed and treated between February 2009 and June 2018 at our centre were retrospectively analysed in this study. The exclusion criteria were as follows: 1) fusiform, mycotic, and traumatic aneurysms; 2) aneurysm diameter  $\geq$  5 mm; 3) intracranial haemorrhage due to unknown reasons, or inability to identify the location of the ruptured aneurysm among multiple IAs; 4) inability to evaluate aneurysm geometry and morphology with computed tomography angiography/digital subtraction angiography (CTA/DSA); and 5) patients who presented other cerebrovascular diseases such as cerebral arteriovenous malformation, arteriovenous fistula, or moyamoya disease.

### Definition of variables and data collection

The patients' neurologic statuses were established based on retrospective analyses of their medical records. The severity of SAH was assessed with the Fisher Grade (FG) based on computed tomography (CT) imaging, and with the Hunt and Hess (H&H) Grade based on clinical presentation.

Patient-specific characteristics collected in the study are shown in Table 1. Heart comorbidities were defined as coronary heart disease, heart valve disease, arrhythmias, and heart dysfunction. Cerebral ischaemic comorbidities were defined as cerebral infarction, transient ischaemic attack, and cerebral vascular stenosis, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty. In addition, we collected data on aspirin and statins use (excluding patients on dual antiplatelet agents or non-aspirin antiplatelet agents) at the time of diagnosis of the intracranial aneurysms.

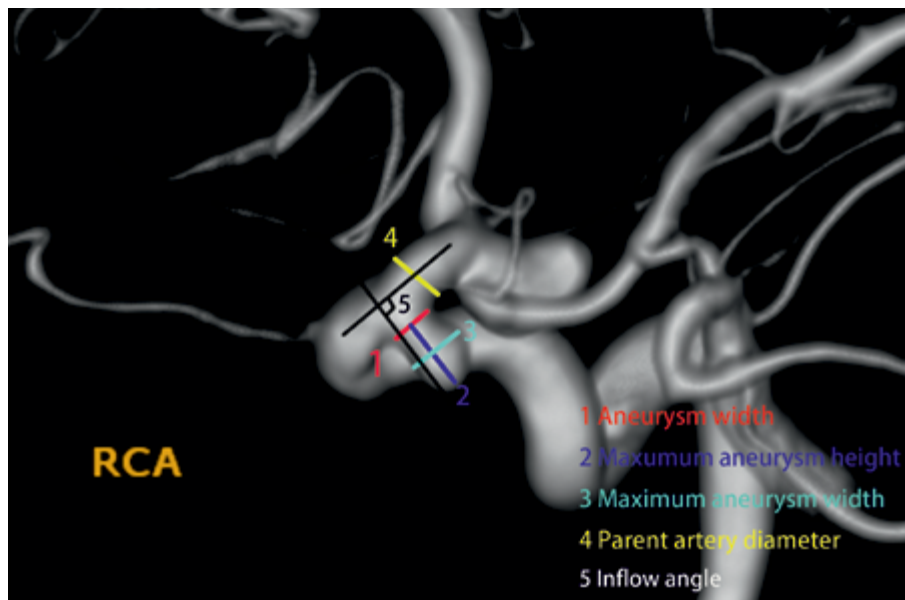
The following morphometric measurements of the aneurysmal characteristics were taken: bifurcation aneurysms (yes/no), multiple IAs (yes/no), irregular shape (yes/no), and location (internal carotid artery rather than the posterior communicating artery/posterior communicating artery/anterior communicating artery/middle cerebral artery/posterior circulation). We also collected the following variables: the size of the aneurysm, the aspect ratio (AR; dome-to-neck ratio), the size ratio (SR), and the inflow angle ( $\geq$  90 degrees/< 90 degrees).

**Table 1.** Basic characteristics of all patients and SIAs

	N (%)
No.	160
Female	83 (51.9)
Age < 50 (years)	69 (43.1)
Hypertension	81 (50.6)
Diabetes mellitus	12 (7.5)
Hypercholesterolemia	10 (6.3)
History of stroke	11 (6.9)
Previous SAH	7 (4.4)
Cardiovascular diseases	9 (5.6)
Smoking	54 (33.8)
Alcohol use	41 (25.6)
Aspirin use	20 (12.5)
Statins use	17 (10.6)
Inflow angle < 90 degrees	88 (55.0)
Irregular shapes	99 (69.7)
Aneurysm size (< 3 mm)	49 (30.6)
Multiple aneurysms	17 (10.6)
AR (mean $\pm$ SD)	1.34 $\pm$ 0.83
SR (mean $\pm$ SD)	1.70 $\pm$ 0.77
<b>Location</b>	
ICA	23 (14.4)
ACoA	58 (36.3)
PCoA	36 (22.5)
ACA	12 (7.5)
MCA	9 (5.6)
PC	22 (13.8)
Location of bifurcation	122 (73.6)
<b>H&amp;H grade</b>	
0	3 (1.9)
1	81 (50.6)
2	50 (31.3)
3	19 (11.9)
4	6 (3.8)
5	1 (0.6)
<b>FG</b>	
1	4 (2.5)
2	79 (49.4)
3	51 (31.9)
4	26 (16.3)

SD — standard deviation; AR — aspect ratio; SR — size ratio; PCoM — internal carotid-posterior communicating artery; ACoA — anterior communicating artery; MCA — middle cerebral artery; ICA — internal carotid artery; PC — basilar tip and basilar-superior cerebellar artery AND vertebral artery-posterior inferior cerebellar artery and vertebralbasilar junction; ACA — anterior cerebral artery

Bifurcation aneurysms were defined as aneurysms located at the parent artery bifurcations (anterior communicating artery, internal carotid artery terminus, posterior communicating artery, middle cerebral artery bifurcation, and the apex of the



**Figure 1.** Aneurysm parameter definitions

basilar artery). Size ratio (SR) was defined as the maximum aneurysm height/average of the parent diameter. The aspect ratio (AR) was defined as the ratio of the maximum perpendicular height to the average neck diameter. Inflow angle was defined as the angle between the axis of flow in the parent vessel at the level of the aneurysm neck and the aneurysm's main axis from the centre of the neck to the tip of the dome (Fig. 1).

All morphological parameters were based on three-dimensional CTA/DSA imaging results and evaluated by two experienced neurosurgeons.

### Statistical analysis

The data used in this study was analysed using SPSS software (SPSS 23.0, Chicago IL, USA). Data was analysed using frequencies (percentages) for categorical variables and mean  $\pm$  SD for continuous variables. Data relating to categorical variables was analysed with Fisher's exact test or the Pearson chi-square test. Data relating to continuous variables was analysed using the Mann-Whitney U test or Student's *t*-test. Unconditional logistic regression analysis was used to calculate univariate and multivariate odds ratios (ORs) with 95% confidence intervals (CI). A *P*-value  $< 0.05$  was regarded as statistically significant.

## Results

### Study population

A total of 160 patients (84 women and 76 men) with ruptured SIAs ( $< 5$  mm) were retrospectively analysed in this study. Thirty-two patients were excluded for the following reasons: inability to identify the location of the ruptured aneurysm in multiple IAs ( $n = 17$ ); dissecting, fusiform or traumatic aneurysm ( $n = 10$ ); or aneurysms that were related to

a cerebral arteriovenous malformation, arteriovenous fistula, or moyamoya disease ( $n = 5$ ). Baseline characteristics of all patients and SIAs are shown in Table 1.

### Univariate analyses

In univariate analysis, the following covariates met our previously determined level of significance and entered the forward stepwise selection for the unconditional logistic model: previous SAHs ( $P < 0.006$ ), smoking ( $P = 0.007$ ), alcohol use ( $P = 0.048$ ), aspirin use ( $P = 0.001$ ), inflow angle  $< 90$  degrees ( $P = 0.053$ ), aneurysm size ( $\geq 3$  mm,  $< 5$  mm) ( $P = 0.102$ ), and a higher SR ( $P = 0.001$ ) (Tab. 2).

Factors that were significantly associated with a higher FG (3–4) were smoking ( $P = 0.019$ ), aspirin use ( $P = 0.031$ ), inflow angle  $< 90$  degrees ( $P = 0.011$ ), and aneurysm size ( $\geq 3$  mm,  $< 5$  mm) ( $P = 0.039$ ) (Tab. 3).

### Multivariate analyses

In the final adjusted multivariate analysis, the following covariates met our previously determined level of significance and entered the forward stepwise selection for the unconditional logistic model: previous SAH (OR, 12.245, 95% CI, 2.261–66.334,  $P = 0.004$ ), aspirin use (OR, 4.677, 95% CI, 1.392–15.718,  $P = 0.013$ ), alcohol use (OR, 3.392, 95% CI, 1.146–10.045,  $P = 0.027$ ), inflow angle  $< 90$  (OR, 3.881, 95% CI, 1.273–11.831,  $P = 0.017$ ), and higher SR (OR, 6.611, 95% CI, 2.235–19.560,  $P = 0.001$ ) were independent risk factors for a higher H&H grade in ruptured SIAs (Tab. 2).

In the final adjusted multivariate analysis, smoking (OR, 2.157, 95% CI, 1.061–4.384,  $P = 0.034$ ), and inflow angle  $< 90$  (OR, 2.603, 95% CI, 1.324–5.115,  $P = 0.006$ ) were independent risk factors for a higher FG (3–4) (Tab. 3).

**Table 2.** Univariate analysis and multivariate analysis between H&H 1–2 group and H&H 3–5 group

Characteristic	H&H 1–2	H&H 3–5	Univariate analysis	Multivariate analysis	
			P	OR	P
Female	74 (55.2)	9 (34.6)	0.085		
Age < 50 (years)	60 (44.8)	14 (53.8)	0.520		
Hypertension	67 (50.4)	14 (53.8)	0.832		
Diabetes mellitus	10 (7.5)	2 (7.7)	1.000		
History of stroke	9 (6.8)	2 (7.7)	0.146		
Previous SAH	4 (3.0)	5 (19.2)	0.006	12.245 (2.261–66.334)	0.004
Cardiovascular diseases	7 (5.3)	1 (3.8)	1.000		
Smoking	39 (29.1)	15 (57.7)	0.007		
Alcohol use	30 (22.4)	11 (42.3)	0.048	3.392 (1.146–10.045)	0.027
Aspirin use	11 (8.2)	9 (34.5)	0.001	4.677 (1.392–15.718)	0.013
Statins use	12 (9.0)	5 (19.2)	0.133		
Inflow angle < 90 degrees	69 (51.5)	19 (73.1)	0.053	3.881 (1.273–11.831)	0.017
Irregular shapes	94 (70.7)	20 (76.9)	0.637		
Aneurysm size ( $\geq 3$ mm, < 5 mm)	89 (66.4)	22 (84.6)	0.102		
Multiple aneurysms	15 (11.2)	2 (7.7)	1.000		
AR (mean $\pm$ SD)	1.37 $\pm$ 0.85	1.18 $\pm$ 0.70	0.287		
SR (mean $\pm$ SD)	1.69 $\pm$ 0.75	2.22 $\pm$ 0.78	0.001	6.611 (2.235–19.560)	0.001
<b>Location</b>					
ICA	20 (14.9)	3 (11.5)	0.696		
ACoA	47 (35.1)	11 (42.3)			
PCoA	30 (22.4)	6 (23.1)			
ACA	9 (6.7)	3 (11.5)			
MCA	9 (6.7)	0 (0)			
PC	19 (14.2)	3 (11.5)			
Bifurcation	101 (75.0)	21 (80.8)	0.800		

## Discussion

In this study, the main finding was that inflow angle affected both the higher H&H grade (3–5) and the FG (3–4). In addition, aspirin use, previous SAH, alcohol use, and higher SR were independent risk factors for a higher H&H grade in ruptured SIAs. Smoking was an independent risk factor for a higher FG (3–4). Therefore, the clinical management of small (< 5 mm) unruptured IAs with these underlying factors should be more comprehensive and should be carried out more cautiously.

Inflammation plays a major role in the formation, progress, and rupture of IAs; several anti-inflammatory drugs have been tested for their potential to decrease IA formation and rupture [14, 16–19]. Aspirin has emerged as the most promising medical therapy for decreasing the incidence of aneurysmal subarachnoid haemorrhage by counteracting proinflammatory pathways and stabilising aneurysmal walls [17, 18]. Several population-based studies that have studied the association between antiplatelet therapy and subarachnoid haemorrhage (SAH) have had conflicting results. The International Study

of Unruptured Intracranial Aneurysms (ISUIA) 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, suggesting that frequent aspirin use may have a protective effect on blood vessels [20]. Along similar lines, Garcia Rodriguez et al., using data from the health improvement network, reported a lower risk of SAH with long-term aspirin intake [19]. In contrast, the use of low-dose aspirin has been associated with an increased risk of SAH in the first month after starting treatment [21]. A recent meta-analysis of seven studies suggests an increased risk of aSAH among short-term (< 3 months) aspirin users [15]. The exact mechanism by which aspirin may exert its effects on aneurysm prognosis and rupture is unclear. Recent studies have shown that aspirin (e.g. acetylsalicylic acid) may stabilise aneurysm walls and counteract proinflammatory pathways [14, 22]. In addition, walls of ruptured IAs have higher levels of cyclooxygenase-2 and microsomal prostaglandin E2 synthase 1, both of which are inhibited by aspirin [22]. However, there is little evidence to identify the effect of aspirin use on clinical

**Table 3.** Univariate analysis and multivariate analysis between FRS 1–2 group and FRS 3–4 group

Characteristic	FRS 1–2	FRS 3–4	Univariate analysis		Multivariate analysis	
				P	OR	P
Female	47 (56.0)	36 (47.4)		0.342		
Age < 50 (years)	44 (52.4)	42 (55.3)		0.752		
Hypertension	39 (47.0)	42 (55.3)		0.832		
Diabetes mellitus	6 (7.1)	6 (8.0)		1.000		
History of stroke	4 (4.8)	7 (9.3)		0.351		
Previous SAH	3 (3.6)	6 (7.9)		0.312		
Cardiovascular diseases	3 (3.6)	5 (6.7)		0.477		
Smoking	21 (25.0)	33 (43.4)		0.019	2.157 (1.061–4.384)	0.034
Alcohol use	18 (21.4)	23 (30.3)		0.211		
Aspirin use	6 (7.1)	14 (18.4)		0.031		
Statins use	6 (7.1)	11 (14.5)		0.133		
Inflow angle < 90 degrees	38 (45.2)	50 (65.8)		0.011	2.603 (1.324–5.115)	0.006
Irregular shapes	62 (74.7)	52 (68.4)		0.481		
Aneurysm size ( $\geq 3$ mm < 5 mm)	52 (61.9)	59 (77.6)		0.039		
Multiple aneurysms	9 (10.7)	8 (10.5)		1.000		
AR (mean $\pm$ SD)	1.37 $\pm$ 0.90	1.31 $\pm$ 0.74		0.669		
SR (mean $\pm$ SD)	1.74 $\pm$ 0.87	1.81 $\pm$ 0.67		0.585		
<b>Location</b>						
ICA	16 (19.0)	7 (9.2)		0.696		
ACoA	30 (35.7)	28 (36.8)				
PCoA	15 (17.9)	21 (27.6)				
ACA	4 (4.8)	10 (10.5)				
MCA	7 (8.3)	2 (2.6)				
PC	12 (14.3)	10 (13.2)				
Bifurcation	63 (75.9)	59 (77.6)		0.852		

and radiographic grades of SAH caused by SIAs. In our study, aspirin use was significantly associated with a higher H&H grade in ruptured SIAs, whereas statin use was probably not associated with a higher H&H grade or FG.

Ours is the first study in which aspirin has been significantly associated with higher H&H grades; further studies are needed to determine the safety of aspirin as an emerging potential medical therapy for the prevention of IA rupture.

In the study, we found that inflow angle affected both the higher H&H grade (3–5) and the FG (3–4). Baharoglu et al. evaluated maximal dimension, height–width ratio, and dome–neck aspect ratio sidewall-type aneurysms with respect to the rupture status in a cohort of 116 aneurysms in 102 patients. They found that inflow angle is a significant discriminator of rupture status in aneurysms and is associated with significantly greater peak velocities and kinetic energy transmission to the dome [23]. Tykocki et al. found that inflow angle proved to be a relevant predictor in estimating the aneurysm risk rupture of the posterior cerebral circulation [24]. Similarly, Lv et al. also reported that inflow angle was significantly different between ruptured and unruptured small

posterior communicating artery aneurysms [25]. The most important finding of this study was that inflow angle was the only independent risk factor for both H&H grade and FG. Moreover, for simpler clinical measurements, we divided the inflow angle into  $\geq 90$  degrees /  $< 90$  degrees. In the present study, it was observed that 71.3% of patients with poorer H&H (3–5) had an inflow angle  $< 90$  degrees, and 65.8% of patients with poorer FG (3–4) had an inflow angle  $< 90$  degrees. One possible explanation is that a greater inflow angle leads to an increase of the wall shear stress (WSS), spatial gradient, and results in a more direct flow into the aneurysm dome. These altered blood flow parameters in the aneurysm lumen may increase the risk of aneurysm rupture, and then if bleeding is not quickly stopped after the aneurysm rupture there would be a resultant increase in bleeding volume, and a poorer grade of H&H and FG [26–28].

The importance of the SR has been emphasised in many studies. As a promising new morphological parameter, the SR was first proposed by Dhar et al, when they reported that SR was associated with the rupture of IAs [7]. Several studies have shown a significant relationship between SR and the

risk of rupture of small aneurysms. A study by Kashiwazaki in Japan revealed that SR might predict the risk of rupture in small unruptured IAs [5]. The study of Feng et al. also found that small IAs with larger SRs was associated with a greater rupture risk (OR, 2.766) [29]. However, there have been few studies on the possible mechanisms by which SR increases the risk of rupture. Markus reported that increasing SR aneurysm morphology presented multiple vortices and complex flow patterns and aneurysm luminal area was exposed to low wall shear stress increased with higher SR [30]. Complex flow, multiple vortices, and low aneurysmal wall shear stress have been associated with ruptured IAs in previous studies. These changes may lead to a higher risk of aneurysm rupture. In the present study, a higher SR was an independent risk factor for a higher H&H grade (3–5) in ruptured SIAs (Tab. 2). For two aneurysms of the same size, a high SR indicates a small-sized parent artery. However, the threshold value of SR for predicting aneurysm rupture is unknown, although several previous studies have reported a higher SR value being related to the rupture status of IAs. We found that aneurysms located distally in the anterior cerebral artery and M2/3 of the middle cerebral artery were consistently associated with a higher SR, and that ruptured SIAs at these locations were associated with greater risks of a higher H&H grade. However, a high SR was not significantly associated with a high FG (3–4). A possible reason for this finding is that the diameter of the distal vessel is small or the space around the vessel is small, so the amount of bleeding is small; therefore, the CT image shows a low FG.

AR was first proposed by Ujiie et al. and was defined as aneurysm depth to aneurysm neck width. They found that AR in 88% of ruptured aneurysms was higher than 1.6, while 56% of unruptured aneurysms had an AR lower than 1.6 [31]. A high AR was statistically more likely to have a greater low wall shear stress (WSS) area ratio that causes the dysfunction of the endothelium, which is consistent with the low flow theory [32]. The disruption and dysfunction of endothelial cells caused by non-physiological WSS is an important step in IA formation and rupture [33]. Therefore, a higher AR means a smaller neck and slower intra-aneurysmal blood flow, which reflects a higher risk of rupture. However, in our study, AR was not significantly associated with a high FG or a higher Hunt and Hess scale grade.

Female gender, history of SAH, and cigarette smoking have all been identified as independent risk factors for aneurysm rupture in previous studies [34–36]. In our study, previous SAH was significantly associated with a high Hunt and Hess scale grade, and smoking was significantly associated with a high FG. However, previous SAH was not significantly associated with a high FG, and smoking was not significantly associated with a high Hunt and Hess scale grade. It seems that patients with a history of SAH may have a poor neurological status and do not correlate to the severity of SAH on CT imaging. In this study, alcohol use and aneurysm size ( $\geq 3$  mm,

$< 5$  mm) also had inconsistent performances in the analysis of risk factors for the Hunt and Hess scale and the FG. In order to explore the reasons for this inconsistent performance, we analysed the Spearman's test of correlation between the FG and the Hunt and Hess scale. The results showed that there was a significant correlation between the Fisher grading scale and the Hunt and Hess scale ( $P < 0.001$ ).

### Strengths and limitations

The strengths of our study include the rigorous measurement of parameters by more than two experienced neurologists, therefore ensuring the representativeness and repeatability of the data. Besides, this is the first retrospective and systematic analysis of the risk factors for neurologic status and radiologic extent of subarachnoid haemorrhage (SAH) in small ruptured aneurysms ( $< 5$  mm). This is also the first study in which aspirin use has been significantly associated with a higher H&H grade in ruptured SIAs.

The data generated from this study provides some valuable information that may facilitate the evaluation of the safety of aspirin as an emerging potential medical therapy for preventing IA rupture. However, there were also several limitations to this study.

This study was retrospective in design and all patients were enrolled from a single centre, meaning there was an unavoidable choice bias. Secondly, the Hunt and Hess scale has been reported to have a poor interobserver agreement [36], so the World Federation of Neurosurgical Societies (WFNS) scale was chosen in some studies because of its predictability regarding values. Its application in the clinical environment is very common and convenient [37]. Finally, this study did not explore the effects of the Fisher grading scale and the Hunt and Hess scale on the outcome of ruptured SIAs patients; we will explore this separately in a future research paper.

### Conclusions

In this study, the main finding was that two easily measurable morphological parameters, inflow angle and higher SR, were independent risk factors for the severity of SAH in SRAs. The clinical management of small aneurysms with these factors should be more cautious and comprehensive. Our findings also suggested that aspirin use was significantly associated with a higher H&H grade in ruptured SIAs. To ascertain whether aspirin should be instituted as a prophylactic measure in all patients with unruptured aneurysms requires a randomised controlled trial.

**Conflict of interest:** None declared.

**Data availability statement:** All relevant data is within the paper.

**Ethics:** The study protocol was approved by the institutional review board at our hospital. All patients gave written informed

consent to participate, and the privacy of patients was strictly protected.

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