

Aneurysm characteristics and risk of rebleeding after subarachnoid haemorrhage

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Abstract

Introduction: Knowledge of risk factors for rebleeding after aneurysmal subarachnoid haemorrhage can help tailoring ultra-early aneurysm treatment. Previous studies have identified aneurysm size and various patient-related risk factors for early (≤ 24 h) rebleeding, but it remains unknown if aneurysm configuration is also a risk factor. We investigated whether irregular shape, aspect- and bottleneck ratio of the aneurysm are independent risk factors for early rebleeding after aneurysmal subarachnoid haemorrhage.

Patients and methods: From a prospectively collected institutional database, we investigated data from consecutive aneurysmal subarachnoid haemorrhage patients who were admitted ≤ 24 h after onset between December 2009 and January 2015. The admission computed tomographic angiogram was used to assess aneurysm size and configuration. With Cox regression, we calculated stepwise-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for irregular shape, aspect ratio ≥ 1.6 mm and bottleneck ratio ≥ 1.6 mm.

Results: Of 409 included patients, 34 (8%) patients had in-hospital rebleeding ≤ 24 h after ictus. Irregular shape was an independent risk factor for rebleeding (HR: 3.9, 95% CI: 1.3–11.3) after adjustment for age, sex, PAASH score, aneurysm location, aneurysm size and aspect- and bottleneck ratio. Aspect ratio ≥ 1.6 mm (HR: 2.3, 95% CI: 0.8–6.5) and bottleneck ratio ≥ 1.6 mm (HR: 1.7, 95% CI: 0.8–3.6) were associated with an increased risk of rebleeding, but were not independent risk factors after multivariable adjustment.

Conclusions: Irregular shape is an independent risk factor for early rebleeding. However, since the majority of subarachnoid haemorrhage patients have an irregular aneurysm, additional risk factors have to be found for aneurysm treatment prioritisation.

Keywords

Aneurysm, rebleeding, risk factors, subarachnoid haemorrhage

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Introduction

Rebleeding of a ruptured aneurysm after aneurysmal subarachnoid haemorrhage (aSAH) is associated with poor functional outcome.¹ Guidelines advocate aneurysm treatment as early as possible,² or within 72 h.³ However, ultra-early aneurysm treatment (≤ 24 h) may not lead to improved outcome, or may even be detrimental, if applied to all patients.^{4,5} Risk factors for rebleeding within 24 h after ictus may help tailoring ultra-early aneurysm treatment to those patients with the highest risk of early rebleeding. Previous studies

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found poor clinical condition on admission and aneurysm size as risk factors for rebleeding.^{6–11} In a study on unruptured intracranial aneurysms, aneurysm irregularity was found to be an independent risk factor for aneurysm rupture.¹² Case-control studies comparing unruptured and ruptured intracranial aneurysms showed that aneurysm irregularity and increased aspect- and bottleneck ratio were associated with aneurysm rupture.^{13–15} However, it is unknown if aneurysm configuration is a risk factor for early rebleeding. We aimed to investigate whether aneurysm irregularity and aspect- and bottleneck ratio are independent risk factors for in-hospital rebleeding ≤ 24 h after ictus.

Patients and methods

Study population

The Institutional Review Board of the University Medical Center Utrecht (UMCU) decided that no formal approval needed to be obtained, since this study entails an analysis of available data from routine patient care. Patient data were retrieved from a prospective institutional database from the UMCU, which is a tertiary referral centre for patients with SAH. All patients with a diagnosis of aSAH referred between 17 December 2009 and 1 January 2015 were included. The diagnosis of aSAH was established by subarachnoid blood on the computed tomography (CT) or xanthochromia of the cerebrospinal fluid in combination with the presence of an aneurysm on CT angiography (CTA) or digital subtraction angiography (DSA). Exclusion criteria were: (1) patients with a non-aneurysmal cause of SAH; (2) patients with a fusiform, mycotic or dissecting intracranial aneurysm; (3) hospital admission > 24 h after ictus; (4) recurrent SAH from a previously ruptured aneurysm; (5) time of ictus unknown; (6) absence or insufficient quality of a CTA; (7) CTA slice thickness > 1.0 mm and (8) multiple aneurysms visualised on CTA and uncertainty which aneurysm had ruptured.

Data extraction

Imaging data were reviewed for aneurysm shape, neck, width, length and size. We also collected data on age, sex, time and date of ictus, date of admission, Prognosis on Admission of Aneurysmal Subarachnoid Haemorrhage (PAASH) score,¹⁶ location of the aneurysm, time and date of aneurysm treatment and time and date of rebleeding occurrence ≤ 24 h after ictus. Since we aimed to identify risk factors for rebleeding ≤ 24 h after ictus, we included in our dataset only instances of rebleeding that occurred ≤ 24 h after ictus. Rebleeding was defined as a sudden clinical

deterioration with signs of increased haemorrhage on the subsequent CT scan. In intubated and sedated patients in whom a CT scan to confirm the suspicion of rebleeding was not performed because of the limited clinical consequences, rebleeding was defined as a sudden increase in blood pressure with fresh blood suddenly coming out of the external ventricular drain. The time of rebleeding was based on either the start of clinical symptoms or the confirmation by a CT scan if time of symptom onset was unclear.

Measurements of aneurysm characteristics

The shape of the aneurysm was dichotomised into regular and irregular. An aneurysm was considered irregular if blebs, multiple lobes or aneurysm wall protrusions were present.¹³ If such irregularities were present due to the peri-aneurysmal environment, the aneurysm was also considered irregular. Length was defined as the maximum distance between the centre of the aneurysm neck to the aneurysm dome, width as the maximum width of the aneurysm perpendicular to the aneurysm length and size as the maximum aneurysm diameter (online supplementary material Figure 1). Additional details on aneurysm measurements are given in the online supplementary material. Cut-off values for aspect- and bottleneck ratio were determined in advance and based on previous studies.^{13,17} Since bottleneck ratio has only been investigated as a continuous variable, we based the bottleneck cut-off score on aspect ratio studies.^{13,17} Aspect ratio (length/neck) was categorised into three categories (< 1.3 mm, 1.3–1.5 mm and ≥ 1.6 mm) and bottleneck ratio (width/neck) into two categories (< 1.6 mm and ≥ 1.6 mm). One author (IK), who was masked for clinical information, performed all aneurysm measurements and determined whether the aneurysm was irregular after being trained by an experienced neuro-interventional radiologist (IvdS). In case of doubt, the aneurysm measurements or the shape of the aneurysm was reviewed by an experienced neuro-interventional radiologist (IvdS) during a consensus meeting ($< 10\%$ of aneurysms).

Statistical analysis

Kaplan Meier curves were generated for time to occurrence of rebleeding ≤ 24 h. Data were censored if aneurysm treatment or death occurred. If more than one episode of rebleeding occurred, we used the time to the first rebleeding. Cox proportional hazard regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). HRs were stepwise-adjusted in different models. In model 1, we adjusted for age, sex and PAASH score. In model 2, we additionally adjusted for the location of the aneurysm,

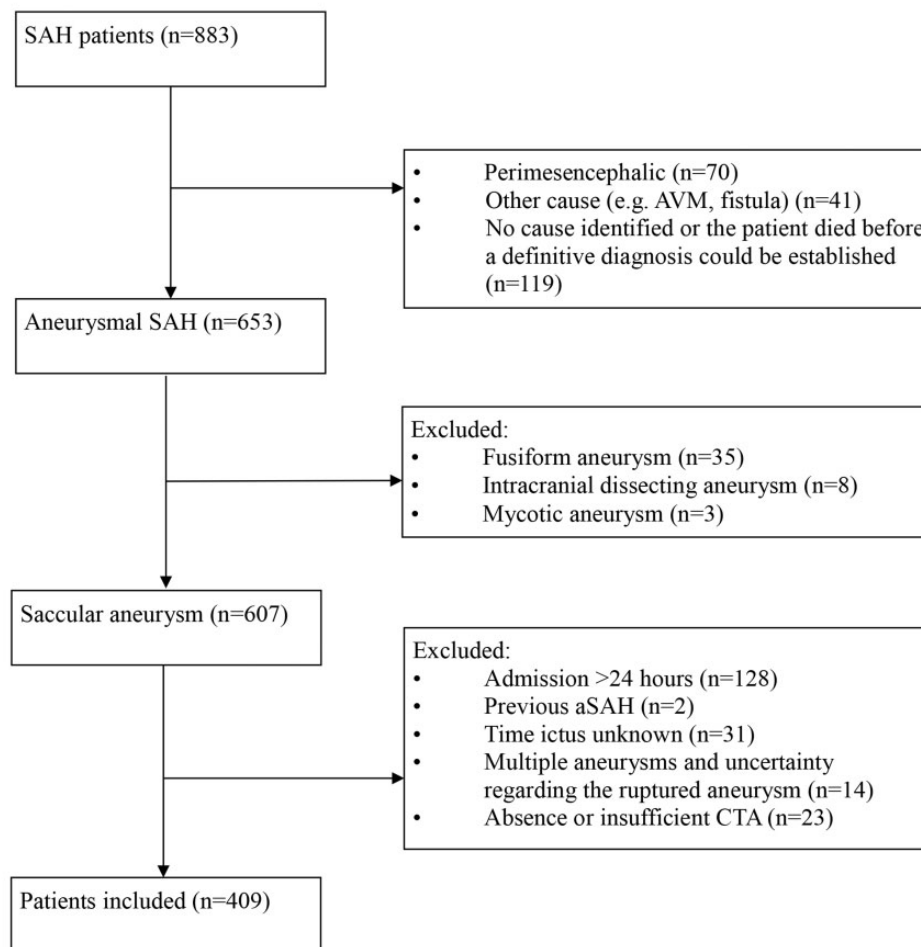


Figure 1. Patient flowchart.

SAH: subarachnoid haemorrhage; aSAH: aneurysmal subarachnoid haemorrhage; AVM: arteriovenous malformation; CTA: computed tomography angiography.

aneurysm size, aneurysm shape, aspect- and bottleneck ratio. Analyses were performed with the prespecified aspect- and bottleneck categories and with aspect- and bottleneck ratio as continuous variables.

Results

We included 409 patients (Figure 1). Patient- and aneurysm characteristics are shown in Table 1 for patients with and without rebleeding. PAASH score could not be determined for four intubated patients.

The ruptured aneurysm was treated ≤ 24 h in 180 patients (44%). Rebleeding ≤ 24 h occurred in 34 (8%) patients. In 32 patients, the episode of rebleeding fulfilled the criteria of a sudden clinical deterioration with signs of increased haemorrhage on the subsequent CT scan. In two patients, the episode of rebleeding fulfilled the criteria of a sudden increase in blood

pressure with fresh blood suddenly coming out of the external ventricular drain. Rebleeding occurred in 30/256 patients (12%), with an irregular aneurysm and in 4/153 (3%) with a regular aneurysm. In total, 256 patients (63%) had an irregular aneurysm. The Kaplan-Meier curves illustrate cumulative rebleeding incidence rates within 24 h (Figure 2(a)) and according to aneurysm shape, aspect- and bottleneck ratio (Figure 2(b) to (d)). In univariable analyses, aneurysm shape, aspect- and bottleneck ratio ≥ 1.6 mm were risk factors for rebleeding ≤ 24 h (Table 2). In multivariable analysis, irregular aneurysm shape remained an independent risk factor (HR 3.9, 95% CI: 1.3–11.3) after adjustment for age, sex, PAASH score, location of the aneurysm, aneurysm size, aspect- and bottleneck ratio. Aspect ratio (≥ 1.6 vs. < 1.3 mm; HR 2.3, 95% CI: 0.8–6.5) and bottleneck ratio (≥ 1.6 vs. < 1.6 mm; HR 1.7, 95% CI: 0.8–3.6) were associated with an increased risk

Table 1. Patient- and aneurysm characteristics.

	All patients N = 409 (%)	Patients with rebleeding ≤ 24 h N = 34 (%)	Patients without rebleeding ≤ 24 h N = 375 (%)
Female sex (%)	294 (72)	27 (79)	267 (71)
Mean age (SD)	57 (13)	58 (12)	57 (13)
Mean PAASH score (SD) ^a	2 (1)	3 (1)	2 (1)
Anterior aneurysm location (%)	346 (85)	28 (82)	318 (85)
Aneurysm size in mm (%)			
≤ 4.9	111 (27)	3 (9)	108 (29)
5.0–6.9	96 (24)	4 (12)	92 (25)
7.0–9.9	100 (24)	12 (35)	88 (24)
≥ 10.0	102 (25)	15 (44)	87 (23)
Irregular aneurysm shape (%)	256 (63)	30 (88)	226 (60)
Aspect ratio (%)			
< 1.3	149 (36)	5 (15)	144 (38)
1.3–1.5	81 (20)	7 (21)	74 (20)
≥ 1.6	179 (44)	22 (65)	157 (42)
Bottleneck ratio (%)			
≥ 1.6	146 (36)	21 (62)	125 (33)

SD: standard deviation.

^aPAASH score could not be determined in four intubated patients.

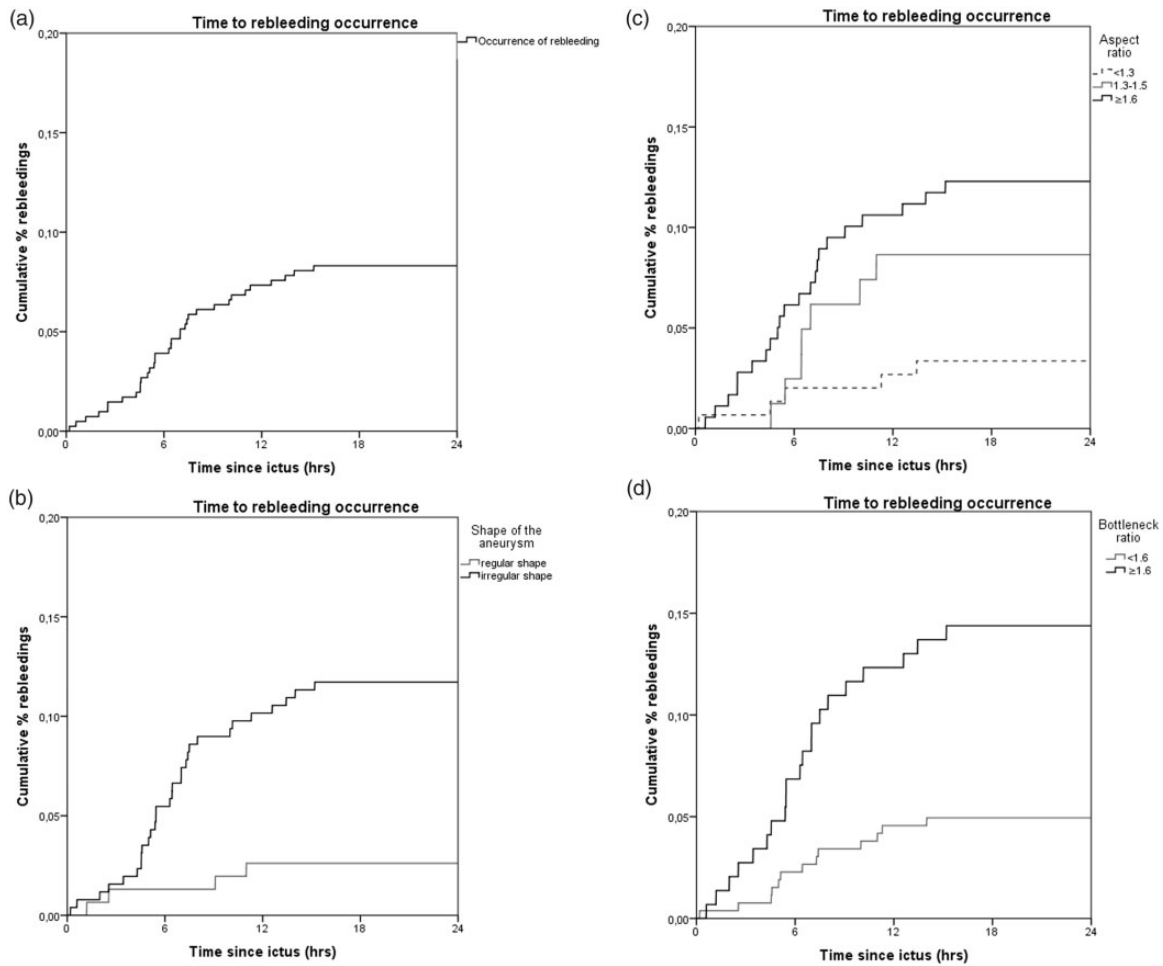


Figure 2. Kaplan-Meier one minus survival curves of time to rebleeding occurrence (a); according to the shape of the aneurysm (b); aspect ratio (c); and bottleneck ratio (d).

Table 2. Aneurysm characteristics and risk of rebleeding ≤ 24 h.

	Rebleeding incidence, %	Crude HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Aneurysm shape				
Regular	3	Ref	Ref	Ref
Irregular	12	4.7 (1.6–13.2)	4.9 (1.7–14.1)	3.9 (1.3–11.3)
Aspect ratio				
<1.3	3	Ref	Ref	Ref
1.3–1.5	9	2.6 (0.8–8.2)	2.8 (0.9–8.7)	2.5 (0.8–8.0)
≥ 1.6	12	3.8 (1.5–10.1)	3.7 (1.4–5.7)	2.3 (0.8–6.5)
Bottleneck ratio				
<1.6	5	Ref	Ref	Ref
≥ 1.6	14	3.2 (1.6–6.3)	2.8 (1.4–5.7)	1.7 (0.8–3.6)

Note: Model 1: HR adjusted for sex, age and PAASH score. Model 2: HR adjusted for sex, age, PAASH score, location of the aneurysm, aneurysm size, aneurysm shape, aspect- and bottleneck ratio.

Ref: reference value; PAASH: Prognosis on Admission of Aneurysmal Subarachnoid Haemorrhage; HR: hazard ratio; CI: confidence interval.

of rebleeding, but both were not independent risk factors after multivariable adjustment (Table 2). Aspect- and bottleneck ratio as continuous variables were also not independently associated with rebleeding (data not shown).

Discussion

This study shows that irregular aneurysm shape is an independent risk factor for rebleeding ≤ 24 h after ictus. Aspect- and bottleneck ratio were also associated with an increased risk of rebleeding but were not independent risk factors.

So far, no other studies have investigated aneurysm configuration as potential risk factors for rebleeding ≤ 24 h after ictus. One study assessed aneurysm wall surface irregularity, aspect- and bottleneck ratio as potential predictors for rebleeding before aneurysm treatment.¹⁸ In that study, only 17% of the included patients were admitted to the hospital ≤ 24 h after ictus. Aneurysm wall surface irregularity was identified as an independent predictor for rebleeding. Aneurysm height, aspect- and bottleneck ratio were not independent predictors for rebleeding. Another study investigated whether the presence of an aneurysmal bleb was associated with rebleeding, but no association was found in contrast to our results.¹⁹ A plausible explanation for this discrepancy is that our study used a wider definition for aneurysm irregularity, namely the presence of blebs, multiple lobes or aneurysm wall protrusions.

Studies on aneurysm haemodynamics provide a possible explanation for the increased risk of rebleeding in irregularly shaped aneurysms.^{20–22} Increased wall shear stress has been suggested to induce localised wall damage and eventually bleb formation.^{20,21} In addition, aneurysmal blebs showed higher pulsatile

forces.²² We hypothesise that localised wall damage and high pulsatile forces result in rupture and rebleeding of irregularly shaped aneurysms.

A different pathophysiological mechanism may underlie the increased risk of rebleeding in patients with a high aspect- or bottleneck ratio. These ratios are higher if the aneurysm is more elongated or if the dome is broader in comparison to the neck. Since the size of the neck determines the in- and outflow into the aneurysm, the blood flow will be more turbulent than pulsating, rendering a low flow in aneurysms with a high aspect- or bottleneck ratio.^{23,24} The low blood flow in the aneurysm has been hypothesised to cause disruption of the aneurysm wall integrity possibly leading to rupture and rebleeding.^{23,24}

A strength of our study is that we performed multi-variable analyses in which we accounted for patient- and aneurysm-related variables. In addition, since we investigated risk factors for rebleeding ≤ 24 h after ictus, we included in our dataset only patients with instances of rebleeding that had occurred ≤ 24 h after ictus. Risk factors for rebleeding ≤ 24 h may differ from risk factors for rebleeding > 24 h after ictus, also with regard to their morphological characteristics. Another strength of our study is that one author performed all aneurysm measurements to rule out interobserver variation, and that this author was masked for the occurrence of rebleeding at time of aneurysm assessment. A limitation is that the observed proportion of patients with rebleeding is probably an underestimation, since we did not include events of sudden clinical deterioration suspicious for rebleeding before a head CT scan was obtained. A second limitation is that inaccurate classification of rebleeding could have occurred in intubated and sedated patients in whom a head CT scan confirming the suspicion of rebleeding was not performed. A sudden increase in blood pressure may

occur due to other complications than rebleeding and it can be difficult to determine whether it is fresh blood or cerebrospinal fluid mixed with old blood coming out of the external ventricular drain. A more accurate definition of rebleeding for these patients would have been 'an increase in intracranial pressure in addition to fresh blood suddenly coming out of the external ventricular drain'. Unfortunately, intracranial pressure measurements were not routinely recorded and thus we do not have these data available. A third limitation is that 5% of the aneurysm measurements were performed on a CTA made at the referring hospital. The difference in quality of the CTA performed at the referring hospital might have resulted in less precise measurements for these patients. Also, the external validity is limited since aneurysm configuration was assessed once by one author; thus, we have no data on inter- and intraobserver variability. Although we had to exclude one-third of our patients with aSAH because of various reasons, we still had sufficient statistical power to assess the three determinants describing aneurysm configuration. Lastly, we based the bottleneck cut-off score on previous aspect ratio studies. Depending on the distribution of rebleeding events in our sample, this may have influenced our results. However, in both models, aspect- and bottleneck ratio as continuous variables were also not independently associated with rebleeding. Cut-off scores were used since, in our opinion, these are easier to use in clinical practice for aneurysm treatment prioritisation than a continuous scale.

Although irregular shape of the aneurysm is an independent risk factor for early rebleeding, we need additional risk factors for aneurysm treatment prioritisation, since two-thirds of the patients without rebleeding also has an irregular aneurysm. To identify the optimal candidates for ultra-early aneurysm treatment, larger studies are needed to develop risk prediction models to determine absolute risks for early rebleeding and risks of complications of ultra-early treatment.

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Declaration of Conflicting Interests

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Informed consent

Written informed consent was not sought for the present study because the Institutional Review Board of the UMCU waived informed consent.

Ethical approval

Ethical approval for this study was waived by the Institutional Review Board of the UMCU because it concerns a retrospective analysis of data obtained during routine clinical care.

Guarantor

MV.

Contributorship

MV conceptualised the project and drafted the study protocol. IK performed aneurysm measurements, collected and analysed data and drafted the manuscript. JG contributed to the statistical analysis. IvdS trained IK on performing aneurysm measurements and reviewed measurements in case of doubt. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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