Survival Analysis of Risk Factors for Major Recurrence of Intracranial Aneurysms after Coiling

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ABSTRACT: *Background:* Recurrence after intracranial aneurysm coiling is a highly prevalent outcome, yet to be understood. We investigated clinical, radiological and procedural factors associated with major recurrence of coiled intracranial aneurysms. *Methods:* We retrospectively analyzed prospectively collected coiling data (2003-12). We recorded characteristics of aneurysms, patients and interventional techniques, pre-discharge and angiographic follow-up occlusion. The Raymond-Roy classification was used; major recurrence was a change from class I or II to class III, increase in class III remnant, and any recurrence requiring any type of retreatment. Identification of risk factors associated with major recurrence used univariate Cox Proportional Hazards Model followed by multivariate regression analysis of covariates with $P < 0.1$. *Results:* A total of 467 aneurysms were treated in 435 patients: 283(65%) harboring acutely ruptured aneurysms, 44(10.1%) patients died before discharge and 33(7.6%) were lost to follow-up. A total of 1367 angiographic follow-up studies (range: 1-108 months, Median [interquartile ranges (IQR)]: 37[14-62]) was performed in 384(82.2%) aneurysms. The major recurrence rate was 98(21%) after 6(3.5-22.5) months. Multivariate analysis (358 patients with 384 aneurysms) revealed the risk factors for major recurrence: age > 65 y (hazard ratio (HR): 1.61; $P = 0.04$), male sex (HR: 2.13; $P < 0.01$), hypercholesterolemia (HR: 1.65; $P = 0.03$), neck size $\geq$4 mm (HR: 1.79; $P = 0.01$), dome size $\geq$7 mm (HR: 2.44; $P < 0.01$), non-stent-assisted coiling (HR: 2.87; $P = 0.01$), and baseline class III (HR: 2.18; $P < 0.01$). *Conclusion:* Approximately one fifth of the intracranial aneurysms resulted in major recurrence. Modifiable factors for major recurrence were choice of stent-assisted technique and confirmation of adequate baseline occlusion (Class I/II) in the first coiling procedure.

RÉSUMÉ: Analyse de survie des facteurs de risque de récidive majeure après occlusion endovasculaire d'anévrismes intracrâniens. *Contexte:* Une récidive après l'occlusion endovasculaire d'un anévrisme survient fréquemment, sans qu'on ne s'explique pourquoi. Nous avons examiné les facteurs cliniques, radiologiques et procéduraux associés à la récidive majeure d'anévrismes intracrâniens après occlusion endovasculaire. *Méthode:* Nous avons analysé rétrospectivement les données prospectives concernant les patients traités par occlusion endovasculaire entre 2003 et 2012. Nous avons recueilli les caractéristiques des anévrismes, des patients et les techniques opératoires utilisées, avant le congé hospitalier ainsi que le suivi angiographique après l'occlusion. La classification Raymond-Roy a été utilisée: une récidive majeure était définie comme un changement de la classe I ou II à la classe III, une augmentation résiduelle de classe III et une récidive nécessitant tout type de réintervention. Les facteurs de risque associés à une récidive majeure ont été identifiés au moyen du modèle des risques proportionnels de Cox suivi d'une analyse de régression multivariée des covariables, $p < 0,01$. *Résultats:* Au total, 467 anévrismes ont été traités chez 435 patients: 283 patients (65%) présentaient une rupture aiguë de l'anévrisme, 44 patients (10,1%) sont décédés avant le congé hospitalier et 33 (7,6%) ont été perdus au suivi. En tout, 1367 études angiographiques de suivi (écart de 1 à 108 mois ; médiane 37 ; écarts interquartiles de 14 à 62 mois) ont été effectuées pour 384 anévrismes (82,2%). Le taux de récidive majeure a été de 21% (98) après 6 mois (3,5 à 22,5 mois). L'analyse multivariée (358 patients porteurs de 384 anévrismes) a montré que les facteurs de risque d'une récidive majeure étaient: l'âge > 65 ans (risque relatif (RR): 1,61 ; $p = 0,04$), le sexe masculin (RR: 2,13 ; $p < 0,01$), l'hypercholestérolémie (RR: 1,65; $p = 0,03$), la taille du collet de l'anévrisme $\geq$ 4mm (RR: 1,79 ; $p = 0,01$), la taille de l'anévrisme $\geq$7mm (RR: 2,44 ; $p < 0,01$), l'endoembolisation assistée par stent (RR: 2,87 ; $p = 0,01$) et une classe III initiale (RR: 2,18 ; $p < 0,01$). *Conclusion:* Environ un anévrisme intracrânien sur cinq a donné lieu à une récidive majeure. Les facteurs modifiables d'une récidive majeure étaient le choix d'une technique assistée par stent et la confirmation d'une occlusion initiale adéquate (classe I/II) lors de la première embolisation endovasculaire.

Endovascular treatment with coiling techniques are widely used for ruptured and unruptured intracranial aneurysms[1,2]. Retreatment, rupture or rerupture of coiled aneurysms can lead to worsening in clinical status and are potential undesired outcomes associated with recurrence after endovascular treatment[3].

The overall post coiling recurrence rates have been reported at 15%–34% in several studies[4-6]. A meta-analysis suggested that major recurrence occurred in 20.8%[95% confidence interval (CI), 19.8%–21.9%] requiring retreatment in 10.3% [95% CI, 9.5%–11.0%] of coiled aneurysms[7]. In part due to its high prevalence, aneurysm recurrence represents the main weakness of endovascular coiling

relative to surgical clipping. Hence, detailed analysis is of critical importance to achieve effective prevention of aneurym recurrence.

The currently known potential risk factors associated with post-coiling recurrence include large aneurysm size[8], presence of intraluminal thrombus[9], low packing density[10-12], initial incomplete occlusion[5,13-16], duration of follow-up[5,17], ruptured status at presentation[5,18,19], location in the posterior circulation[7,14,20,21], neck width size >4 mm[22], and unfavorable dome-to-neck ratio[4]. However, the available literature analyzing post-coiling recurrence has limitations such as lack of data on individual patients or individual aneurysms (due to mostly aggregated data being available), limited sample size, high rate of incomplete follow-up, wide variation in the schedule and modality of angiographic follow-up, limited heterogeneity in the location, status, types and the sizes of the aneurysms studied, and inconsistent definition of recurrence[7]. These limitations may have halted previous survival analyses.

The primary goal of this study was to identify risk factors for major recurrence after the coiling procedure of intracranial aneurysms. Secondary goals were to explore the frequencies of recurrence, rupture, rerupture and retreatment of aneurysms after coiling treatment.

METHODS

Patients

We prospectively collected data from patients presenting with ruptured or unruptured intracranial saccular aneurysms treated with endovascularly-deployed detachable coils between January 2003 and July 2012. We excluded parent vessel occlusion, flow-related aneurysms and flow diverting techniques. Clinical and demographic data included age, sex, smoking history within five years, treated/non-treated systemic hypertension, treated/non-treated hypercholesterolemia, history of subarachnoid hemorrhage (SAH), hydrocephalus, as well as Hunt & Hess, World Federation of Neurosurgical Societies (WFNS) and Fisher grades at treatment date. This study was approved by our local ethics board.

Aneurysms and periprocedural status

Aneurysm data included location, shape, rupture status, dimensions and the presence of incorporated arteries. Based on the artery of origin, we classified location into anterior (anterior communicating artery [AcomA], posterior communicating artery [PcomA], anterior cerebral artery [ACA], internal carotid artery [ICA], middle cerebral artery [MCA]) and posterior (basilar tip [BTip], non-basilar tip [nBTip]) circulations. We defined an aneurysm as *ruptured* if SAH was confirmed by non-contrast computed tomography (CT) scan and/or cerebrospinal fluid (CSF) analysis ≤30 days before coiling. In procedures with multiple aneurysms coiled the most likely SAH culprit was labeled as ruptured. Dome size (millimeters distance between the margin of the neck and the fundus) and neck size, periprocedural vasospasm, intraprocedural aneurysm perforation and thromboembolic events were recorded using three-dimensional, diagnostic subtraction angiography (3D-DSA). Using CT scan we recorded the presence of periprocedural hydrocephalus.

Interventional techniques

Endovascular treatment used general anesthesia and systemic heparinization (activated clotting time: 200-400 seconds). After femoral arterial access, aneurysms received detachable coils under biplane fluoroscopy and roadmapping (Axiom Artis, Siemens,

Erlangen, Germany) while employing three dimensional rotational angiogram (3D-DSA). When an artery originated directly from the aneurysm sac or neck (incorporated artery), a residual part of the aneurysm was left untreated to maintain the vessel patency. We used a combination of detachable coils from several manufacturers, including bare platinum and modified or coated coils. When protection of the parent or incorporated vessel was not possible with conventional techniques, or when there was intraprocedural perforation, non-detachable balloons were employed. If balloon remodeling technique was not feasible or unsuccessful, or in presence of unfavorable neck morphology, or in case of intraprocedural coil prolapse, we chose stent-assisted technique. In elective procedures with expected use of a microstent, we initiated dual antiplatelet therapy five to seven days prior, using aspirin (81 mg daily) and clopidogrel (75 mg daily). In the case of emergent need for a stent, we used a loading dual-antiplatelet dose.

Baseline/pre-discharge and follow-up aneurysm occlusion

For optimal inter-observer agreement[23] the interpretation of pre-discharge/baseline and follow-up degree of aneurysm occlusion in DSA and/or magnetic resonance angiography (MRA) was performed using the Raymond-Roy classification (class I: complete/adequate occlusion; class II: residual neck/near complete/ adequate occlusion; class III: residual body/incomplete/inadequate occlusion). The interpretation was non-blinded and performed in random order by the authors (MPdS, CL, DI, HL), in accordance to our customary practice. Any discrepancy was resolved by consensus. Allowing absence of contra-indication for MRI, a pre-discharge/baseline MRA was obtained in all aneurysms treated after 2006 following a change in practice.

Angiographic follow-up

The angiographic follow-up protocol of all aneurysms consisted of one study performed two to three months after the procedure, followed by studies performed every 12 ± 1 months for five years. Subsequently, the angiographic follow-up was repeated every two to five years.

Recurrence, mortality, and retreatment

Major recurrence was any change from class I/II to class III or an increase in size of a class III aneurysm remnant. *Minor recurrence* was the interval change in classes I → II. *Presumed thrombosis* was any change from class II/III to I, or from class III to II, or reduction in the size of a class III remnant.

Lost to follow-up were patients/aneurysms that did not receive an angiographic follow-up after hospital discharge. *Pre-discharge mortality* was death related to the aneurysm in the same hospital admission. *Late mortality* was any death occurring after hospital discharge.

Not every aneurysm with major recurrence was retreated, due to either the patient's non-compliance or medical reasons (i.e. unfavorable post coiling anatomy, significantly elderly patients, or with serious, unstable medical conditions).

Statistical methods

Descriptive data are presented as percentages, means ± standard deviations (SD) for normally distributed variables, and medians ± interquartile ranges (IQR) for non-normally distributed variables.

For differences in categorical variables, Chi-Sq Test or Fisher's exact test was used. If all assumptions were met for parametric analyses of the continuous variables, the 2-sample t-test was used; otherwise the 2-sample Wilcoxon Rank Sum test was applied. The survival analysis methodology studied the detection of major recurrence and its timing in months from treatment. Patients without major recurrence were censored at the time of the last angiographic follow-up or death. Kaplan-Meier method estimated distribution of time to major recurrence. Analysis of annual rate of rerupture post coiling included all the lost to follow-up patients. Univariate and multivariate analyses of major recurrence automatically excluded pre-discharge deaths and patients lost to follow-up. The Cox regression analysis was performed to determine the predictors of major recurrence (hazard ratio with 95% CI). The effects with probability value < 0.1 in the univariate analysis were selected for a multivariate model. All statistical tests were 2-sided and the results were considered significant at $\alpha < 0.05$ (SAS System for Windows version 9.2, SAS Institute, Inc., Cary, North Carolina).

RESULTS

Patients' characteristics, treatment history and retreatment

A total of 467 intracranial aneurysms (286[61%] ruptured and 181[39%] unruptured) in 435 patients (female: 320[74%]; male: 115[26%]) with a mean(SD) age of 55.3(12.4) years (y) met the inclusion criteria (Table 1). First-time coiling after neurosurgical clipping was performed in 16(3.4%) aneurysms (ruptured:eight). Twenty-eight (6.4%) patients had two aneurysms coiled, and two (0.5%) patients had three aneurysms coiled. A total of 15.5% of the aneurysms with dome/neck ratio ≤2 were coiled with a stent, versus 5.5% of the aneurysms with dome/neck ratio >2 (P < 0.01). A total of seven ruptured aneurysms (3%) were treated with stent-assisted coiling as a bailout precaution. The baseline occlusion was not significantly different between coiling techniques (P = 0.78).

Thirty-five (7.5%) aneurysms (ruptured: 23) were coiled twice and four (0.8%) aneurysms (ruptured: three) were coiled thrice during our study period, totaling 510 coiling procedures. The coiling retreatment happened after 2-52 months of the first coiling treatment (Median[IQR]: 9.5[6-14]). Twenty-two retreated major recurrences (56% of 39) had a major recurrence after a second coiling. Of the remainder 17 retreated major recurrences, 13(33%) remained stable, one showed presumed thrombosis, one showed minor recurrence, and two were lost to follow-up. A third coiling was performed in four (10.2% of 39) aneurysms that showed increase in class III remnant during follow-up (10-83 months, Median[IQR]: 24[14-45]).

The retreatment rate per year was 5.25% (95% CI, 3.70-7.24) in the ruptured subcohort and 2.55% (95% CI, 1.48-4.08) in the unruptured subcohort.

Baseline aneurysm occlusion

In the baseline angiography (230 DSA and 237 MRA), we detected class I occlusion in 196(42%) aneurysms, class II in 191 (41%) aneurysms, and class III in 80(17%) aneurysms (Table 1).

Lost to follow-up cases, mortality, and rerupture

Thirty-three (7.6%) patients were lost to follow-up (37 aneurysms; 25 ruptured (8.7%); P = 0.27). Pre-discharge mortality was recorded in 44(10.1% of the entire cohort) patients harboring 46 aneurysms, among which 42 were originally ruptured and two originally unruptured (Table 1). The two pre-discharge mortality cases in the unruptured aneurysms subcohort resulted from intraprocedural perforations representing 1.3% of our unruptured subcohort. Among the subcohort of 79 patients harboring 80 aneurysms with baseline class III occlusion, eleven (13.5%) died before discharge (all originally ruptured) and four (5.0%) were lost to follow-up (all originally ruptured).

Twenty-two (5%) patients suffered late mortality; the cause and date of death was identified in 17/22(77.3%) patients (Median [IQR]: 40[14-61]months) - two were aneurysm related in-patients with multiple untreated aneurysms.

There were no pre-discharge reruptures in the entire cohort. Three (0.8%) aneurysms (all initially ruptured in patients with major recurrence in angiographic follow-up), presented with rerupture, after 3, 38 and 81 months, without mortality. We identified the yearly rerupture rate: 0.43% (95% CI, 0.09-1.25) in the ruptured subcohort and 0.22% (95% CI, 0.04-0.64) in the entire cohort.

Angiographic follow-up and risks factors for recurrence

For the 384(82.2%) followed aneurysms, the total number of angiographic studies was 1367, performed 1-10 times (Mean[SD]: 3.6[2.0]; Median[IQR]: 3[2-5]) for each aneurysm after 1-108 months (Mean[SD]: 40.0[28.6]; Median[IQR]: 37[14-62]). The distribution of the time interval elapsed between the treatment and the last angiographic follow-up for each aneurysm is shown in the Figure.

Stability in occlusion was sustained in 183 aneurysms (39.2% of the entire cohort; 47.6% of the followed-up subcohort) up to a Median(IQR) of 38.5(19-61) months. Fifty-four aneurysms (11.6% of the entire cohort; 14.1% of the followed-up subcohort) demonstrated presumed thrombosis over 28.5(16-60) months.

Any recurrence, either minor or major, was reported in 147(31.5%) aneurysms after a Median(IQR) of 33(7-61) months, of which 14(3.0% of entire cohort) happened following an initial phase of presumed thrombosis (Median[IQR]: 40[36-55] months after coiling).

Major recurrence was seen in 98(21%) aneurysms after six (3.5-22.5) months among which five(1%), two ruptured and three unruptured, happened following an initial phase of presumed thrombosis (Median[IQR]: 72[53-101] months after coiling). The five cases that presented with delayed major recurrence after presumed thrombosis represented increase in class III remnant and had unfavorable dome/neck and width/neck ratio.

Regarding the subcohort with baseline class III remnant (80 aneurysms in 79 patients), sixty-five (81.2%) were followed. Increase in class III remnant/major recurrence was shown in 25(31.5%) aneurysms, presumed thrombosis in 22(27.5%), stability in 10(12.5%), post-thrombosis major recurrence in 4(5%), and post-thrombosis minor recurrence in 4(5%). In this subcohort, major recurrence was detected after a median (IQR) of six (3.5-9) months, while post-thrombosis major recurrence took 86.5(67.5-102.5) months to appear.

The univariate and multivariate survival analyses censored 77 patients with a total of 83 aneurysms (representing 44 pre-discharge deaths and 33 patients lost to follow-up). In total, 384 aneurysms in 358 patients were assessed in these analyses. Univariate survival analysis of major recurrence as the primary

Table 1: Patients and Aneurysms Characteristics

Patients	SAH(%)[*]	No SAH(%)	Total	P
	283(65)	152(35)	435	
Age	55.4 ± 13.3	55.3 ± 10.5	55.3 ± 12.4	0.52
Female	203(71.7)	117(77)	320(73.6)	0.24
Male	80(28.3)	35(23)	115(26.4)	
Pre-discharge Mortality	42(14.8)	2(1.3)	44(10.1)	<0.01
Lost to Follow-up	24(8.5)	9(5.9)	33(7.6)	0.34
Post-discharge All Mortality	10(3.5)	12(7.9)	22(5)	
Aneurysm-related	1(0.3)	1(0.7)	2(0.5)	
Not Aneurysm-related	6(2.1)	9(5.9)	15(3.4)	
Undetermined Mortality	3(1.1)	2(1.3)	5(1.1)	

Aneurysms	Ruptured(%)	Unruptured(%)	Total	
	286(61)	181(39)	467	
Location				
Anterior Circulation	213(74.5)	133(73.5)	346(74)	<0.01
ACA/AcomA	117(41)	25(14)	142(30)	
ICA	24(8.5)	70(38.5)	94(20)	
PcomA	56(19.5)	21(11.5)	77(17)	
MCA	16(5.5)	17(9.5)	33 (7)	
Posterior Circulation	73(25.5)	48(26.5)	121(26)	
BTip	46(16)	37(20.5)	83(18)	
nBTip	27(9.5)	11(6)	38(8)	
Size (mm)				
Dome	7.2 ± 3.5	8.0 ± 4.0	7.5 ± 3.7	0.01
Neck	3.2 ± 1.3	3.8 ± 1.7	3.4 ± 1.5	<0.01
Dome/Neck ratio	2.3 ± 0.8	2.1 ± 0.9	2.2 ± 0.8	0.01
Technique				
Conventional	184(64)	80(44)	264(56.5)	0.78
Balloon-assisted	95(33)	59(33)	154(33)	
Stent-assisted	7(3)	42(23)	49(10.5)	
Baseline Occlusion				
Class I	106(37)	90(50)	196(42)	0.02[†]
Class II	127(44.5)	64(35)	191(41)	
Class III	53(18.5)	27(15)	80(17)	0.31[††]
Major Recurrence	63(22)	35(19.3)	98(21)	0.49

[*]SAH = Subarachnoid hemorrhage; ACA/AcomA = anterior cerebral artery/anterior communicating artery; ICA = internal carotid artery; PcomA = posterior communicating artery; MCA = middle cerebral artery; BTip = basilar tip; nBTip = non-basilar tip; mm = millimeters. [†]Baseline occlusion result is statistically different between ruptured and unruptured aneurysms; [††]Baseline Class III occlusion result was not statistically different between ruptured and unruptured aneurysms.

outcome (Table 2) showed that age >65 y (hazard ratio (HR): 1.84; P < 0.01), male sex (HR: 2.34; P < 0.01), hypercholesterolemia (HR: 2.26; P < 0.01), rupture at presentation (HR: 1.55; P = 0.03), aneurysm neck size ≥4 mm (HR: 2.23; P < 0.01), dome size ≥7 mm (HR: 3.17; P < 0.01), dome to neck ratio >2 (HR: 1.69; P = 0.01), Fisher grade 4 (HR: 1.77; P < 0.01), conventional and balloon-assisted versus stent-assisted coiling (HR: 2.12; P = 0.02), class III occlusion at the baseline angiography (HR: 2.76; P < 0.01) and using MRA versus DSA as the baseline angiography (HR: 1.76; P < 0.01) were associated with major recurrence. Among the aneurysms with dome to neck ratio >2, both the ones with neck ≥4 mm (HR: 1.95; P = 0.02) and the ones with neck <4 mm (HR: 1.99; P = 0.02) were associated with major recurrence. Trend association with major recurrence (0.05 < P < 0.1) was identified for systemic hypertension (HR: 1.44; P = 0.07).
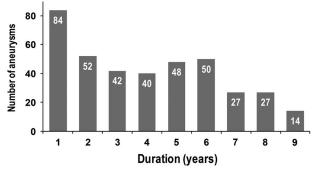
Figure: Distribution of the time interval elapsed between the treatment and the last angiographic follow-up for each aneurysm.

In the multivariate model (Table 2) we excluded the variables dome/neck ratio >2 (due to the results of the univariate analysis) and Fisher grade 4 (due to its sole reference to the ruptured aneurysms). After multivariate Cox regression analysis, age >65 y (HR: 1.61; P = 0.04), male sex (HR: 2.13; P < 0.01), hypercholesterolemia (HR: 1.65; P = 0.03), aneurysm neck size ≥4 mm (HR: 1.79; P = 0.01), aneurysm dome size ≥7 mm (HR: 2.44; P < 0.01), non-stent-assisted coiling (HR: 2.87; P = 0.01) and baseline occlusion of class III (HR: 2.18; P < 0.01) were risk factors associated with major recurrence.

DISCUSSION

Recurrence after coiling is an outcome with unknown clinical significance, notwithstanding potential association with a higher rate of rupture, rerupture and retreatment[6,15,18,20,24]. To enable prevention it is critical to understand associated risk factors and the type of recurrence post coiling that is associated with poor clinical outcome. The main challenge lies in the fact that the definition of "recurrence" varies greatly in the literature. This variability generates a wide range of recurrence rates and results with considerable range in its association with multiple potential risk factors[5,8-22]. We applied a strict definition of recurrence and major recurrence and analyzed the relationship between several clinical, anatomical and technical data as a surrogate of major recurrence using survival analysis. The strength of our study rests upon the use of survival analysis in a large, long follow-up series, enabling a relatively more reliable assessment of multiple covariates.

The baseline/pre-discharge angiographic imaging in our study showed class III remnant in less than one fifth of aneurysms. In a systematic review of 46 similar studies, inadequate baseline occlusion was reported in 9% of aneurysms[7], while prospective multicenter studies with independent core laboratories reported inadequate baseline occlusion in 20-29%[25,26]. Such a discrepancy in the degree of baseline occlusion among the studies likely originates from the subjectivity of the occlusion grading and from the heterogeneous inclusion criteria or angiographic follow-up modalities used in the studies. The 3-grade Raymond-Roy scale is pragmatically used by most authors to assess aneurysm occlusion after coiling. However, the performance and limitations of this classification for recurrence assessment has been outlined[27] particularly in the case of interval increase in class III remnant[28,29]. Nevertheless, in an attempt to optimize inter- and intra- observer

agreement, the majority of the studies published to date classified the post-coiling occlusion using similar scale.

When distinguishing minor from major recurrences, our analysis found major recurrence in approximately one fifth of the aneurysms, which is comparable to the literature[5,7]. Baseline class III remnant was associated with major recurrence and this was similar to others[5,30,31,32]. Our study confirms that major recurrence can occur several months after coiling procedure. It also shows the usefulness of close angiographic follow-up within the first year after coiling with baseline class III remnant to detect major recurrence.

Aneurysm location did not significantly impact major recurrence in our study, a finding which was similar to that of others[5,18]. However, association between posterior circulation location and impending recurrence was found in a series with the majority of ruptured aneurysms[33] and in studies focusing on posterior circulation aneurysms[7].

In agreement with the literature, dome ≥7 mm and neck ≥4 mm were associated with major recurrence. However, dome/neck ratio >2 was associated with major recurrence in the univariate analysis which is not in line with the literature[5,30-35]. This is explained by dome/neck ratio ≤2 being significantly more frequent in our unruptured subcohort while representing an indication for stent placement in our center (selection bias). Compared to other studies[5,30,34,35], ours has a relatively higher percentage of stent-assisted procedures. Even though the baseline degree of occlusion was not different among our three types of coiling technique, this multivariate analysis shows that stent-assist technique protects aneurysms against major recurrence, similar to prior studies[17,36]. Stent assisted coiling (SAC) technique adds invasiveness and potential morbidity to a coiling procedure. A large case series reported more lethal complications in patients treated with SAC technique compared with non-SAC cases[17]. The rates of major recurrence in SAC, along with its comparative disadvantages such as procedure-related complications and mortality,[17,36] require further investigation in large series and in prospectively controlled trials such as the ongoing Stenting in Aneurysm Treatment (STAT) trial[37].

In our series, none of the SAH-related variables (Fisher, Hunt &Hess and WFNS grades), periprocedural hydrocephalus or vasospasm could predict major recurrence. Overall similar results have been found in other series[30,31].

In our practice, the coiling treatment of unruptured aneurysms in elderly patients is typically reserved to large, symptomatic, morphologically complex, or unstable aneurysms, and in those patients with multiple aneurysms or significant family history. Older age (>65 years) was significantly associated with major recurrence and some of our indications for coiling may have influenced the association with major recurrence (selection bias). There is sparse literature on the effects of older age in the durability of coiling procedures[38].

Male sex was a factor associated with major recurrence. Contrary to other studies[5,30,33], our male patients were 2.1 times more likely to present with major recurrence. Our analysis showed a trend for our male patients to have larger aneurysm dome size than females. We found however no significant difference comparing covariates between males and females and no interaction between sex and each of the significant risk factors identified in the multivariate analysis. One study in elderly patients treated with coiling found an association between male sex and rupture/ rerupture post coiling[38].

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Table 2: Major Recurrence Predictors – Survival Analysis

Potential Predictors		Univariate Analysis		Multivariate Analysis	
		Hazard Ratio (95%CI)	P	Hazard Ratio (95%CI)	P
Age	>65yo	1.84(1.18-2.87)	<0.01	1.61(1.01-2.55)	0.04
Sex	Male	2.34(1.55-3.54)	<0.01	2.13(1.40-3.26)	<0.01
Smoking	Yes	1.15(0.77-1.71)	0.49	-	-
Hypertension	Yes	1.44(0.96-2.15)	0.07	1.08(0.69-1.69)	0.73
Hypercholesterolemia	Yes	2.26(1.49-3.43)	<0.01	1.65(1.04-2.62)	0.03
Presentation	Ruptured	1.55(1.02-2.34)	0.03	1.50(0.94-2.32)	0.08
Aneurysm Neck Size	≥4 mm	2.23(1.50-3.32)	<0.01	1.79(1.12-2.86)	0.01
Aneurysm Dome Size	≥7 mm	3.17(2.06-4.88)	<0.01	2.44(1.49-3.99)	<0.01
Dome/Neck Ratio	>2	1.69(1.12-2.53)	0.01	Removed	-
Aneurysm Shape	Unilobular	1.04(0.68-1.57)	0.86	-	-
Aneurysm Location	Post.* vs ACA/AcomA	1.25(0.74-2.09)	0.40	-	-
	Post. vs ICA/PComA	1.40(0.86-2.29)	0.17	-	-
	Post. vs MCA	1.10(0.48-2.50)	0.82	-	-
	Post. vs Ant.[†]	1.31(0.85-2.00)	0.21	-	-
	BTip[‡] vs non-BTip Post.	1.36(0.61-3.05)	0.45	-	-
	Post./PComA vs Others	1.11(0.80-1.54)	0.53	-	-
Incorporated Artery	Yes	1.42(0.84-2.39)	0.19	-	-
Multiple Aneurysms	Yes	1.05(0.70-1.59)	0.78	-	-
Fisher Grade[§]	4	1.77(1.16-2.70)	<0.01	Removed	-
Hunt & Hess Grade[§]	3-4	1.33(0.77-2.31)	0.30	-	-
WFNS Grade[§]	4	1.58(0.80-3.14)	0.19	-	-
Periproc.[#] Hydrocephalus[§]	Yes	1.06(0.64-1.74)	0.82	-	-
Periproc. Vasospasm[§]	Yes	1.17(0.76-1.78)	0.47	-	-
Periproc. Vasospasm[‖]	Yes	1.18(0.75-1.84)	0.47	-	-
Technique	No Stent	2.12(1.12-4.05)	0.02	2.87(1.19-6.90)	0.01
Intraproc**. Perforation	Yes	0.75(0.27-2.04)	0.57	-	-
Intraproc. Thromboembolism	Yes	1.00(0.46-2.16)	0.99	-	-
Baseline Occlusion	Class III	2.76(0.77-4.78)	<0.01	2.18(1.23-3.85)	<0.01
Baseline Modality	MRA	1.76(1.15-2.67)	<0.01	1.32(0.85-2.05)	0.21

ACA/AcomA = anterior cerebral artery/anterior communicating artery; ICA = internal carotid artery; PcomA = posterior communicating artery; MCA = middle cerebral artery; BTip = basilar tip; nBTip = non-basilar tip; mm = millimeters. MRA = magnetic resonance angiography; Periproc = ; Intraproc = ; WFNS = World Federation of Neurosurgical Societies *Post = Posterior; [†]Ant = Anterior; [‡]Basilar Tip; [§]Ruptured aneurysms only; [‖]All aneurysms; [#]Periprocedural; **Intraprocedural

Along with elderly age, hypercholesterolemia was an atherosclerosis-related risk factor for major recurrence. Our data are insufficient to clarify whether hypercholesterolemia or its treatment with statins exerts the risk inducing effect[39] and these have yet to be investigated in further studies.

No significant association between systemic hypertension and major recurrence could be established in our cohort, perhaps due to our routine of strict blood pressure control after the procedure. Smoking was not associated with major recurrence and this finding was similar to the mid-term follow-up results of the CLARITY study on ruptured aneurysms[31], although contrary to retrospective data[40].

Rupture at presentation was not associated with major recurrence. We found no significant difference between the ruptured and unruptured subcohorts in terms of baseline class III remnant. Some authors have shown the association between rupture at presentation with any recurrence in general[18,41] or with major recurrence in particular[5], while others have not[33-35]. The larger dimension of the unruptured aneurysms[7,42] seen in our cohort, with significantly more baseline occlusion class I, is proposed as a possible cause of the lack of such an association.

Emphasizing previous published data[43,44], all the reruptures in our study were documented after the hospital discharge in the originally ruptured subcohort. When investigated at the time of rerupture, these aneurysms met our criteria for major recurrence. The majority of our retreatments happened less than one year after the initial coiling procedure and were approximately twice more frequent in the ruptured aneurysms. For a few reasons a

relationship between class III remnant and pre-discharge mortality could not be established in our study: small number of deaths, with the minority of pre-discharge mortalities having baseline class III remnant and the majority of pre-discharge mortalities happening in the ruptured subcohort. We had a small number of late mortality cases and there was no association between the coiled aneurysm(s) and cause of death.

Our study has important limitations including its observational design, the interchangeable use of DSA and MRA for angiographic follow-up in some patients, the non-blinded random interpretation of the angiographic follow-up (reflecting our customary practice), and the small sample size to establish an association between major recurrence and mortality.

Our study was strengthened by the large cohort of patients, the detailed prospective data collection, the low rate of lost to follow-up, and the relatively regular and long duration of angiographic follow-up.

CONCLUSION

The survival analysis in this large prospective cohort with long term follow-up data identified age >65 y, male sex, hypercholesterolemia, aneurysm neck size ≥4 mm, aneurysm dome size ≥7 mm, non-stent-assisted coiling, and the baseline incomplete occlusion (class III) as risk factors associated with major recurrence. Patients harboring one or more of these features may require a more rigorous and individualized angiographic follow-up schedule. The choice of stent-assisted technique and the confirmation of adequate baseline occlusion were the only modifiable factors in our study. Prospective series are needed to continue the analysis of aneurysm recurrence after endovascular treatment.

DISCLOSURES

Authors have nothing to disclose.

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