Factors Affecting the Outcome of Multiple Intracranial Aneurysm Surgery

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Abstract

Objectives Multiple intracranial aneurysms (MIAs) are fairly common entities. Unless MIAs are incidentally diagnosed, they remain asymptomatic until they rupture. In this study, the authors investigated factors affecting the surgical outcomes in patients with MIA by evaluating the surgical outcomes of 90 consecutive cases.

Material and Methods Medical records were retrospectively reviewed for 409 consecutive cerebral aneurysm cases that underwent surgery in the hospital from 2011 to 2013. The patients' data were prospectively collected. All MIA patients (n = 90) constituted the core sample for this study.

Results The authors detected 221 aneurysms in 90 patients (49 females and 41 males; mean age: 50.8 ± 11.9 years; range: 25–82 years). Of the patients, 67 presented with subarachnoid hemorrhage, whereas 23 were incidentally diagnosed with unruptured aneurysms. The mortality rate was 13.3% (n = 12). The morbidity rate was 18.8% (n = 17). Of the patients, 67.8% (n = 61) had returned to their jobs and normal daily activities by their last follow-up (average: 52.3 months). History of coronary artery diseases (CADs) and low neurologic grade at presentation (Hunt-Hess grade 4/5) are independent risk factors for increasing morbidity and mortality in patients with MIA (odds ratio [OR]: 18.46; p = 0.007); (OR: 30.0; p = 0.002) and (OR: 0.06; p = 0.0001); (OR: 0.07; p = 0.002), respectively.

Conclusion History of CADs and high Hunt-Hess grade are independent risk factors for poor surgical outcomes of patients with MIA.

Keywords
- clipping microsurgical
- coronary artery disease
- multiple intracranial aneurysm

Introduction

Multiple intracranial aneurysms (MIAs) are fairly common entities. Unless MIAs are incidentally diagnosed, they remain asymptomatic until they rupture. Intracranial aneurysm rupture leads to subarachnoid hemorrhage (SAH), a potentially lethal event with a high rate of mortality and morbidity.[1,2]

A systematic review suggested that unruptured cerebral aneurysms occur in up to 6% of the general population.[3] MIAs occur in up to one-third of people with intracranial aneurysms.[4]

Several studies have investigated factors that lead to aneurysm multiplicity. Cigarette smoking, age, and female gender seem to be risk factors for MIAs in patients who have suffered SAH.[5,6] Chronic hypertension may have an impact on vessel wall thickness, leading to aneurysm enlargement and eventual rupture, usually associated with an acute increase in the

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blood pressure. MIAs can present as single aneurysms, and then other aneurysms may develop with time or there may be multiple aneurysms at initial presentation.

The prognosis of aneurysmal SAH has remained poor despite improvements in medical technology and microneurosurgical treatment. The mortality rate for SAH is 30 to 40%, and as many as 60% of those who survive SAH may be functionally dependent.[7] Several studies have investigated the surgical outcome in patients with cerebral aneurysms. The authors investigated factors affecting the surgical outcome in patients with MIA.

Material and Methods

Design of the Study

This retrospective study was approved by the medical ethics committee of the hospital (decision number 573/2015). Written informed consent was obtained from the patients and their first-degree relatives for the publication of their cases and accompanying images.

Patient Data

Medical records were prospectively collected (all entrance data were collected at hospitalization) from 409 consecutive patients with intracranial aneurysm who underwent surgery at the hospital from 2011 to 2013. All patients with MIA, in whom at least one of the aneurysms had been surgically treated, were included in this study. The mean follow-up was 52.3 months. Clinical outcomes were evaluated using the Glasgow outcome scale (GOS).

Surgical Technique

The authors have described their surgical technique for MIAs in detail previously.[8] The important steps are summarized as follows. The conditions in which anatomy permitted unilateral approaches were assessed preoperatively. Ruptured, irregularly shaped, and large aneurysms (good candidates for rupture) were first priorities for repair. Craniotomy should always be performed on the side of the ruptured aneurysm.[8] Under general anesthesia, the patients were placed in the supine position with the head held in a fixation device. In this series, neurosurgeons performed lateral supraorbital craniotomy as a minimally invasive approach for all aneurysms. Single-stage clipping was planned for aneurysms by performing approximately 3 × 3-cm-sized craniotomy (►**Fig. 1**). Additional pericallosal and/or marginally callosal aneurysms were treated with a slightly larger but single craniotomy that extended medially and stopped at the immediate midline for visualization of the interhemispheric fissure.

After suitable craniotomy was performed, the roof and lateral orbital wall were radically thinned to near total. The Sylvian fissure was never opened; this was extremely promising by avoiding unnecessary arterial manipulations. For a middle cerebral artery (MCA) aneurysm, the Sylvian fissure was opened just over the dome and then proximal and distal ends wrier revealed. Further splitting of the fissure up to the carotid artery was not necessary.

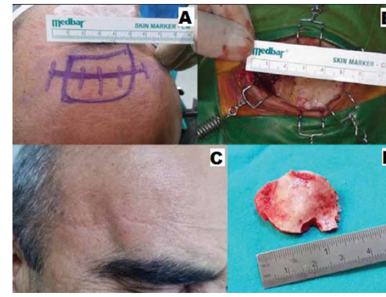

Fig. 1 Lateral supraorbital approach. (**A**) A 5-cm skin incision for left lateral supraorbital craniotomy. (**B**) A 4- × 4-cm operation field was obtained using a 5-cm skin incision for left lateral supraorbital approach. (**C**) Healed incision scar of right lateral supraorbital craniotomy in an MIA case without cosmetic issues on his postoperative 12th month visit. (**D**) A perioperative 3- × 3-cm craniotomy bony flap.

The lamina terminalis was opened in all cases with SAH before beginning aneurysm dissection, except for anteriorly directed anterior communicating artery (ACoA) aneurysms. This allowed for further relaxation of the brain and gaining space as well as for reducing the hydrocephalus risk that may occur secondary to SAH. For nonruptured aneurysms if initial cisternal cerebrospinal fluid (CSF) drainage was satisfactory, postclipping opening of the lamina terminalis was preferred. To avoid unnecessary oozing into the third ventricle during dissection, microsurgical clipping of all reachable aneurysms was performed. Aneurysms that were not appropriate for clipping were wrapped with very thin cotton prepared like a moocher to facilitate fibrosis. Some were sent for endovascular treatment if they could not be clipped.

Statistical Analysis

All data are expressed as the mean ± standard deviation (SD) with the range shown in parentheses. Differences between groups were assessed by a one-way analysis of variance (ANOVA) using the SPSS 21.0 (IBM Inc.) statistical package. Significance in the multivariate model was determined using $p < 0.05$, and trend-level effects were defined as $p = 0.05–0.10$. All p values were presented with an odds ratio (OR).

Results

The authors detected 221 aneurysms in 90 patients (49 females and 41 males; mean age: 50.8 ± 11.9 years; range: 25–82 years). Of the patients, 67 presented with SAH, whereas 23 were incidentally diagnosed with unruptured aneurysms. Sixty-five (72.2%) patients presented with two aneurysms (►**Table 1**). Aneurysms were located in ACoA ($n = 50$), MCA ($n = 94$; right: 49 and left: 45), internal carotid artery (ICA; $n = 49$; right: 34 and left: 15), posterior communicating artery (PCoA; $n = 13$; right: 9 and left: 4), anterior cerebral artery (ACA; $n = 10$; right: 6 and left: 4), basilar artery ($n = 3$), and superior cerebellar artery (SCA; $n = 2$). According to the Hunt-Hess scale in the SAH group, the aneurysms were grades 1, 2, 3, 4, and 5 in 8, 35, 13, 7, and 4 patients, respectively. Comorbidities in all patients are shown in ►**Table 2**. Exception was for two aneurysms that could not be treated because the patients died after treating

Table 1 Number of aneurysms in each patient

Number of aneurysms	Ruptured aneurysms				Unruptured aneurysms			
	Females (*n*)	%	Males (*n*)	%	Females (*n*)	%	Males (*n*)	%
2	25	73.5	26	78.8	8	53.3	6	75.0
3	7	20.6	6	18.2	3	20.0	1	12.5
≥ 4	2	5.9	1	3.0	4	26.7	1	12.5
Total	34	100	33	100	15	100	8	100

Table 2 Comorbidities of the 90 patients

Comorbidities	Ruptured aneurysms				Unruptured aneurysms			
	Females (*n*)	%	Males (*n*)	%	Females (*n*)	%	Males (*n*)	%
Smoking	11	32.6	18	54.5	4	26.7	1	12.5
Hypertension	20	58.8	9	27.3	9	60.0	2	25.0
CAD	6	17.6	1	3.0	0	0	2	25.0
Diabetes mellitus	3	8.8	1	3.0	0	0	1	12.5
COPD	2	5.9	2	6.1	0	0	2	25.0
Thyroid dysfunction	2	5.9	0	0	3	20.0	1	12.5
CVA	1	2.9	1	3.0	1	6.6	1	12.5

Abbreviations: CAD, coronary artery diseases; COPD, chronic obstructive pulmonary diseases; CVA, cerebrovascular accident.
Note: Despite the fact that CAD is usually seen more in men than women, in these patients, it was seen more in women than men. This may be because of the sample size is relatively small. Our hospital is one of four big reference neurosurgery hospitals in our city, and all small hospitals refer their patients for us. This may be another reason.

their ruptured aneurysms. Observation was the choice of treatment in 1.4% ($n = 3$) of all aneurysms, embolization/coiling in 2.3% ($n = 5$), and wrapping in 2.3% ($n = 5$). Twelve (5.4%) aneurysms in three patients were treated via two craniotomies performed at the same stage, 27 (12.2%) in 10 patients were treated in two stages, and 33 (15%) in 11 patients were treated via one craniotomy at the same stage (15 were clipped contralaterally). Total 134 (60.6%) aneurysms detected in 66 patients were clipped microsurgically through ipsilateral craniotomies. Three patients presented with recurrent SAH at 122, 106, and 23 months, respectively after initial curative treatment. Cigarette smoking was an independent risk factor for SAH, but only with trend-level significance (OR, 2.75; $p = 0.053$). However, smoking, when associated with male sex was a risk factor for SAH (OR, 8.4; $p = 0.037$). The mortality rate was 13.3% ($n = 12$). The morbidity rate was 18.8% ($n = 17$). Of these 17 patients, 7 were already partially or completely dependent on others for daily activities preoperatively (GOS ≤ 3). Of the patients, 67.8% ($n = 61$) returned to their jobs and normal daily activities (GOS ≥ 4) at their last follow-up (average: 52.3 months). Complications included hydrocephalus ($n = 9$), hematoma ($n = 2$), CSF leakage ($n = 2$), infarction due to vasospasm ($n = 2$; transient vasospasm cases were not included), seizures ($n = 2$), surgical site infection ($n = 1$), rhinorrhea ($n = 1$), and osteomyelitis ($n = 1$).

Five patients with SAH and one with incidental MIAs had transient vasospasms, but they were documented according to their status at discharge. Female sex increased the mortality rate, but only with trend-level significance (OR, 3.97; $p = 0.068$). However, male sex factor increased the morbidity rate (OR, 3.02; $p = 0.049$). Age was not statistically significant ($p = 0.89$ and $p = 0.79$, respectively). The presence of SAH increased both morbidity and mortality rates, but only with trend-level significance (OR, 3.84; $p = 0.064$) and (OR, 5.63; $p = 0.07$), respectively. Details are shown in ►**Table 3**.

Morbidity (OR, 0.06; $p = 0.0001$) and mortality (OR, 0.07; $p = 0.002$) rates increased in patients with worse neurologic grade SAH. The presence of hematoma increased the mortality rate (OR, 0.16; $p = 0.007$). However, it increased the morbidity rate only with trend-level significance (OR, 0.31; $p = 0.051$). Impairment of consciousness (high Hunt-Hess grades 4/5) increased the mortality rate (OR, 0.18; $p = 0.01$). However, this group did not have a high morbidity risk (OR, 1.66; $p = 0.35$).

Of 61 fully recovered patients (GOS ≥ 4), 23 were heavy smokers (at least smoking ≥ 20 cigarettes a day). Six heavy smokers recovered with deficits (GOS < 3). Of 12 patients who died, 5 were heavy smokers. Therefore, smoking increased the morbidity rate (OR, 0.33; $p = 0.044$). Hypertension also increased the morbidity rate, but only with trend-level significance (OR, 0.40; $p = 0.098$). However, neither smoking (OR, 0.43; $p = 0.16$) nor hypertension (OR, 0.48; $p = 0.22$) had a statistically significant impact on mortality in patients with MIA. History of coronary artery diseases (CADs) increased morbidity and mortality rates (OR, 18.46; $p = 0.007$ and OR, 30.0; $p = 0.002$, respectively; ►**Table 3**).

Similarly, there was no statistically significant impact on morbidity or mortality rates between history of diabetes mellitus (DM; OR, 1.84; $p = 0.53$ and OR, 5.9; $p = 0.12$, respectively), chronic obstructive pulmonary disease (COPD; OR, 0.89; $p = 0.70$ and OR, 1.3; $p = 0.6$, respectively), thyroid dysfunction (OR, 0.89; $p = 0.70$ and OR, 1.3; $p = 0.6$, respectively),

Table 3 Factors affecting the surgical outcomes of MIAs patients

Factor	Recovered group (*n* = 61)	Morbidity group (*n* = 17)	Mortality group (*n* = 12)	*p* Values
Sex				
Female	34 (55.7%)	5 (29.4%)	10 (83.3%)	For mortality (*p* = 0.068)
Male	27 (44.3%)	12 (70.6%)	2 (16.7%)	For morbidity (*p* = 0.*049*)
Age	50.3 ± 11.2 (25–74)	49.9 ± 13.02 (25–82)	52.7 ± 12.6 (33–75)	*p* = 0.89 and *p* = 0.79, respectively
SAH (+) SAH (−) (unruptured)	41 (67.2%) 20 (32.8%)	15 (88.2%) 2 (11.8%)	11 (91.7%) 1 (8.3%)	*p* = 0.064 and *p* = 0.07, respectively
Presence of Hematoma (high Fisher grade [IV])	11 (18%)	7 (41.2%)	7 (58.3%)	For mortality (*p* = 0.*007*), for morbidity (*p* = 0.051)
Impairment or loss of con sciousness (high Hunt-Hess [IV/V])[a]	16 (26.2%)	3 (17.6%)	8 (66.7%)	For mortality (*p* = 0.*01*), for morbidity (*p* = 0.35)
Worsening neurologic grade (high Hunt-Hess [IV/V])[a]	3 (4.9%)	8 (47.1%)	5 (41.7%)	*p = 0.0001* and *p* = 0.*002*, respectively
History of CAD	1 (1.6%)	4 (23.5%)	4 (33.3%)	*p = 0.007* and *p* = 0.*002*, respectively
Cigarette smoking	23 (37.7%)	6 (35.3%)	5 (41.7%)	*p = 0.044* and *p* = 0.16, respectively
History of HT	31 (50.8%)	5 (29.4%)	4 (33.3%)	*p* = 0.098 and *p* = 0.22, respectively
History of DM	2 (3.3%)	2 (11.8%)	1 (8.3%)	*p* = 0.53 and *p* = 0.12, respectively
History of COPD	4 (6.6%)	1 (5.9%)	1 (8.3%)	*p* = 0.7 and *p* = 0.6, respectively
History of thyroid dysfunction	4 (6.6%)	1 (5.9%)	1 (8.3%)	*p* = 0.7 and *p* = 0.6, respectively
History of CVA	2 (3.3%)	1 (5.9%)	1 (8.3%)	*p* = 0.42 and *p* = 0.53, respectively
Posterior circulation aneurysms	2 (50%)	2 (50%)	0	*p* = 0.19 and *p* = 0.7, respectively

Abbreviations: CAD, coronary artery diseases; COPD, chronic obstructive pulmonary diseases; CVA, cerebrovascular accident; DM, diabetes mellitus; HT, hypertension; MIA, multiple intracranial aneurysm.
Note: To see odds ratio (OR) for *p* values in this table look at results in main text.
[a]This comparison was done for SAH group patients.

and cerebrovascular accident (CVA; OR, 2.68; $p = 0.42$ and OR, 1.84; $p = 0.53$, respectively).

Posterior circulation aneurysms were rare in this series; five aneurysms were detected in four patients. Rest of the aneurysms ($n = 216$; detected in 86 patients) were anterior circulation aneurysms. This is due to the tendency to refer posterior circulation aneurysms to the endovascular team. Location in the posterior circulation was not a factor affecting morbidity or mortality ($p = 0.19$ and $p = 0.7$, respectively). Ruptured posterior circulation aneurysms (2/4) with hydrocephalus that was surgically treated had trend-level significance (OR, 9.57; $p = 0.063$).

Discussion

Despite the development of medical instrumentations, techniques, and surgical and endovascular management of patients with MIAs, mortality and morbidity rates remain high and unacceptable. Several studies have shown that after SAH, MIAs are associated with a less favorable outcome than single aneurysms.[5,9] In this study, 67.8% patients had good outcomes. This is close to the experience of all 409 patients (319 with single aneurysms and 90 with MIAs) who underwent surgical treatment for single aneurysms in the same period and at the same institute. Of the 319 patients, 241 recovered fully (GOS ≥ 4), 49 experienced ≥ 1 deficits/morbidities, and 29 died. However, the differences in morbidity and mortality rates were not significant.

Some early prospective studies showed that several factors can affect outcomes of treatment for patients with SAH. Pickard et al[10] suggested that age, sex, loss of consciousness, Glasgow coma scale (GCS) scores, angiographic findings, limb weakness, neck stiffness, hypertension, computed tomography (CT) findings, and treatment factors were individually related to outcome of oral nimodipine use for delayed cerebral infarction of SAH. Rosengart et al[11] suggested that unfavorable outcome after SAH was associated with increasing age, worse neurologic grade, ruptured posterior circulation aneurysm, larger aneurysm size, more SAHs on admission CT, intracerebral/intraventricular hematoma, elevated systolic blood pressure at admission, history of hypertension, myocardial infarction, liver disease, or SAH. These results showed that a history of CADs and low neurologic grade at presentation (Hunt-Hess grade, 4/5) are independent risk factors for increasing mortality and morbidity in patients with MIA. Loss/impairment of consciousness and presentation with hematoma increased the mortality rate, whereas cigarette smoking increased the morbidity rate. Presenting with SAH was also a factor that increased mortality and morbidity rates, but only with trend-level significance. Despite the fact that the authors did not find a relationship between surgical outcome and posterior circulation aneurysms, ruptured posterior circulation aneurysms were associated with a higher rate of hydrocephalus requiring surgical treatment, but only with trend-level significance.

SAH is more common in females than in males (ratio: 2:1). The peak incidence is between 50 and 60 years of age.[12] However, unruptured cerebral aneurysms are as much as three times more common in women.[13] In this study, 23 of 90 MIAs were incidentally diagnosed. This rate is relatively high according to previous reports. This may be because the sample size is relatively small. Our hospital is one of four large reference neurosurgery hospitals in our city, and all small hospitals refer their patients to us. In this series, the female predominance was observed with 54.4% of patients, which was not as high as that in previous reports.[5,12–14] One study found that female sex itself was also associated with an increased rate of MIAs among patients with SAH. The same study suggested that among the elderly (≥ 70 years of age), prognosis was less favorable for patients with SAH with MIAs than for those with a single aneurysm.[6] In this study, female patients had a higher risk for death than male patients, but only with trend-level significance, whereas male patients had a higher deficit risk.

After SAH, the incidence of recurrence within the first 10 years was 22 times higher than that expected in the same population with comparable age and sex. Another study found that smoking, age, and the presence of MIAs at time of SAH were statistically significant risk factors for recurrent SAH.[15] The same study found that 18 (2.4%) of 752 patients had recurrent SAH. In this study, five patients had recurrent MIAs after an average of 70 (23–122) months: three presented with SAH (of 67 patients with SAH; 4.5%) and two presented with headache. All five patients (three women and two men) were heavy smokers. The mean age of the recurrent SAH group was 59.4 ± 5.4 (range: 51–65) years. Thus, the presence of MIAs at the time of SAH and smoking were also statistically significant risk factors for recurrent SAH in these patients. However, advanced age was not a statistically significant risk factor for recurrent SAH. According to these results, presentation with SAH placed these patients with MIAs at higher risk of death or development of new deficits, but only with trend-level significance.

To assess the neurologic grade in patients with SAH, the GCS or Hunt-Hess classification is commonly used. In this study, morbidity and mortality rates were high among patients with MIAs who presented with low neurologic grade (Hunt-Hess 4/5 or < 8 points on GCS). Similarly, a high mortality rate was recorded among those who presented with loss/impairment of consciousness. However, this group was not at risk of suffering a new deficit. A low neurologic grade and history of CAD increased morbidity and mortality rates. Several studies noted the poor prognosis of patients with SAH who present with a low neurologic grade.[6,10,11,16–18] However, to the best of our knowledge, no study has explained the relationship between surgical outcome of aneurysms and history of CAD. Despite the fact that CAD usually occurs in men more than in women, in these patients, CAD occurred in women more than in men. This may be because of the relatively small sample size and the fact that all small hospitals refer their patients to our larger institution. History of CAD is a risk factor for all surgical procedures, and this remained constant for single and multiple aneurysms. This is similar to the experience of all 409 (319 single and 90 MIAs) patients who underwent surgical treatment for a single aneurysm during the same period and at the same institute. Despite the fact that the history of CAD impacts the surgical outcomes in patients with multiple and single aneurysm, the female sex predominance was not apparent in those with a single aneurysm as it was in those with MIAs. Total 35 patients with SAH (19 women [13 single aneurysms] and 16 men [15 single aneurysms]) presented with a history of CAD versus 16 patients with unruptured aneurysms (2 women [2 single aneurysms] and 14 men [12 single aneurysms]).

These results demonstrated that the presence of intracerebral/intraventricular hematoma increased the mortality rate, whereas it increased the morbidity rate only with trend-level significance. Actually, these results are in line with those of previous studies that suggested that the presence of intracerebral/intraventricular hematoma in patients with SAH has a poor prognosis.[10,11,17,18]

Cigarette smoking is known to increase the risk of SAH and spontaneous intracerebral hematoma. It is an independent and the most important risk factor for SAH, which already has been proven in several cohort and case-control studies.[19–22] History of hypertension is considered a risk factor for SAH.[19,20] This study showed that smoking increased the morbidity rate but had no statistically significant impact on mortality in patients with MIAs. History of hypertension increased the morbidity rate, but only with trend-level significance. In addition, multiplicity of aneurysms; surgical treatment approach; and history of DM, COPD, thyroid dysfunction, and CVA factors had no statistically significant impact on morbidity or mortality rates. Three patients with SAH and one with an unruptured MIA had a poor prognosis after surgical complication. The review included these cases.

This study has a few limitations. The sample used comprised all diagnosed and treated cases of MIA at the hospital over 3 years. The sample size was relatively small and did not represent a wide geographic area as all the patients were from Istanbul and surrounding areas. The results represented a single institute experience by the same team of neurosurgeons using lateral supraorbital craniotomy, which is a minimally invasive approach. Other institutes may follow different approaches. The study design was retrospective. Further prospective randomized studies with larger samples and long follow-ups are required to improve the representativeness of the results.

Conclusion

Most prognostic factors for surgical outcome of patients with MIA are present at admission and are not dependent on surgical intervention. History of CADs and high Hunt-Hess grade are independent risk factors for poor surgical outcomes of patients with MIA. Further prospective studies are necessary to systematically investigate these findings.

Conflicts of Interest
There are no financial disclosures or conflicts of interest.

Note
This retrospective study was approved under decision number: (573/2016) by the medical ethics committee of Bakırköy Research and Training Hospital for Neurology Neurosurgery, and Psychiatry (BRSHH) in Istanbul-Turkey.

Name of the Department and Institution in which the work was done: Department of Neurosurgery-BRSHH.

References

1 Broderick JP, Viscoli CM, Brott T, et al; Hemorrhagic Stroke Project Investigators. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stroke 2003;34(6):1375–1381
2 Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G; European Stroke Organization. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis 2013;35(2):93–112
3 Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998;29(1):251–256
4 Baumann F, Khan N, Yonekawa Y. Patient and aneurysm characteristics in multiple intracranial aneurysms. Acta Neurochir Suppl (Wien) 2008;103:19–28
5 Juvela S. Risk factors for multiple intracranial aneurysms. Stroke 2000;31(2):392–397
6 Kaminogo M, Yonekura M, Shibata S. Incidence and outcome of multiple intracranial aneurysms in a defined population. Stroke 2003;34(1):16–21
7 Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 2009;8(7):635–642
8 Asiltürk M, Abdallah A. Clinical outcomes of multiple aneurysms microsurgical clipping: evaluation of 90 patients. Neurol Neurochir Pol 2018;52(1):15–24
9 Rinne J, Hernesniemi J, Niskanen M, Vapalahti M. Management outcome for multiple intracranial aneurysms. Neurosurgery 1995;36(1):31–37, discussion 37–38
10 Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 1989;298(6674):636–642
11 Rosengart AJ, Huo JD, Tolentino J, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. J Neurosurg 2007;107(2):253–260
12 Alg VS, Sofat R, Houlden H, Werring DJ. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. Neurology 2013;80(23):2154–2165
13 Ajiboye N, Chalouhi N, Starke RM, Zanaty M, Bell R. Unruptured cerebral aneurysms: evaluation and management. Sci World J 2015;2015:954954
14 Backes D, Vergouwen MD, Velthuis BK, et al. Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms. Stroke 2014;45(5):1299–1303
15 Wermer MJ, van der Schaaf IC, Velthuis BK, Algra A, Buskens E, Rinkel GJ; ASTRA Study Group. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of existing aneurysms. Brain 2005;128(Pt 10):2421–2429
16 Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968;28(1):14–20
17 Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery 2006;59(1):21–27, discussion 21–27
18 Jiménez-Roldán L, Alén JF, Gómez PA, et al. Volumetric analysis of subarachnoid hemorrhage: assessment of the reliability of two computerized methods and their comparison with other radiographic scales. J Neurosurg 2013;118(1):84–93
19 Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. Stroke 1992;23(9):1242–1249
20 Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. Stroke 1993;24(5):639–646
21 Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 2005;36(12):2773–2780
22 Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke 2002;33(5):1321–1326