Functional outcome 1 year after aneurysmal subarachnoid hemorrhage due to ruptured intracranial aneurysm in elderly patients

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TITLE

FUNCTIONAL OUTCOME 1 YEAR AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE DUE TO RUPTURED INTRACRANIAL ANEURYSM IN ELDERLY PATIENTS.

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Abstract

Background

Population aging raises questions about extending treatment indications in elderly patients with aneurysmal subarachnoid hemorrhage (aSAH). We therefore assessed functional status 1 year after treatment.

Methods

This study involved 310 patients, aged over 70 years, with ruptured brain aneurysm, enrolled between 2008 and 2014 in a prospective multicenter trial (FASHE study: NCT00692744) but considered unsuitable for randomization and therefore analyzed in the observational arms of the study: endovascular occlusion (EV), microsurgical exclusion (MS) and conservative treatment. The aims were to assess independence, cognition, autonomy and quality of life (QOL) at 1 year post-treatment, using questionnaires (MMSE, ADLI, IADL, EORTC-QLQ-C30) filled in by independent nurses after discharge.

Results

The 310 patients received the following treatments: 208 underwent EV (67.1%), 54 MS (17.4%) and 48 were conservatively managed (15.5%). At 1 year, independence rates for patients admitted with good clinical status (WFNS I-III) were, according to the aneurysm exclusion procedure (EV, MS or conservative), 58.9%, 50% and 12.1% respectively. MMSE score was pathological in 26 of the 112 EV patients (23.2%), 10 of the 25 MS patients (40%) and 4 of the 9 patients treated conservatively (44%), without any statistically significant difference [Pearson's χ^2 test, F ratio = 4.29; p = 0.11]. Regarding QoL, overall score was similar between the EV and MS cohorts, but significantly lower with conservative treatment.

Conclusion

Elderly patients in good clinical condition with aSAH should be treated regardless of associated comorbidities. Curative treatment (EV or MS) reduced mortality without increasing dependence, in comparison with conservative treatment.

Key-words

Intracranial aneurysm - Subarachnoid hemorrhage – Elderly – Quality of Life – Autonomy.

Introduction

Population aging in Western countries raises questions about extending treatment indications in elderly patients with aneurysmal subarachnoid hemorrhage (aSAH). According to retrospective studies, natural history and clinical outcome at 3 months after endovascular coiling (EV) (1-11) or microsurgical clipping (MS) (6, 7, 11-16) are favorable only in 50-60% of patients older than 70 years. Of note, this trend is also confirmed in patients in their 8th or 9th decade of life (17-20). Widespread of interventional neuroradiology has made EV treatment predominant over MS, especially in light of guidelines issued following the International Subarachnoid Aneurysm Trial (ISAT) studies (22-25). However, of MS treatment still has a role to play in this category of patients according to post-hoc analysis of the ISAT database in a subgroup of subjects older than 65 years of age (6). Widening treatment indications for ruptured aneurysm to the elderly and, more importantly, deciding between EV or MS treatments obviously requires better understanding of the outcome and likely future that can be expected for patients. So far, no prospective studies have analyzed cognitive outcome, autonomy and quality of life (QOL) following aSAH in this age group. These are significant research questions in a society so strongly centered around the well-being of its members.

The FASHE (French Aneurysmal Subarachnoid Hemorrhage in the Elderly collaborative group) trial (ClinicalTrials.gov identifier NCT00692744, Rouen University Hospital, Protocol Recorded 2007/042 / HP) was a multicenter standard-care study (2008-2014) aiming to randomize subjects over 70 years of age and compare functional outcome at 1 year after EV vs. MS treatment. Initial results in 41 randomized patients among the 351 eligible patients revealed no difference between the 2 arms (26). Hence, the steering committee decided to cease randomization, leaving the remaining 310 patients outside the original trial, but included and analyzed in 3 longitudinal prospective observational cohorts according to type of treatment (EV, MS, or conservative).

The objective of the current study was to prospectively evaluate (by an independent observer) the above outcome measures (independence, cognitive, autonomy, and quality of life) of these 310 patients at 1 year.

Patients and methods

Study design

A multicenter prospective observational longitudinal study conducted in 14 French hospital centers (Besançon, Bordeaux, Caen, Clermont-Ferrand, Dijon, Grenoble, Lille, Lyon, Marseille, Nancy, Nice, Paris Kremlin-Bicêtre, Poitiers, Rennes, Rouen, Toulouse), enrolled only patients above 70 years of age, admitted between November 1, 2008 and October 30, 2012 for ruptured intracranial aneurysm responsible for SAH. This was a clinical standard-of-care study according to the French law of August 9, 2004 (application March 9, 2007) (ClinicalTrials.gov identifier: NCT00692744, Rouen University Protocol Hospital, 2007/042 / HP), no modifying the standard practices of the participating teams.

The primary objective was to assess the proportion of patients with modified Rankin Scale score (mRS) ≤ 2 (independent) at 1 year in each of the 3 prospective cohorts. The secondary objectives were to assess cognitive performance, autonomy and quality of life at 1 year. Quality control throughout the trial was conducted by a Clinical Research Associate, who continued to supervise the analytical process after the trial was closed in November 2013, and made the database available in September 2015 for further subgroup analysis.

Population

Patients met the following inclusion criteria: 1) age ≥70 years; 2) subarachnoid hemorrhage (SAH) diagnosed by CT or lumbar puncture, classified according to the World Federation of Neurological Surgeons (WFNS) scale and dichotomized as good (WFNS I-III) or poor (WFNS IV) general clinical status on admission (27); 3) confirmation of ruptured intracranial aneurysm on cerebral angiography or CT angiography; 4) consensus in the multidisciplinary neurovascular team (neuro-anesthetist, interventional neuroradiologist and neurosurgeon) regarding optimal treatment of the aneurysm: coiling by EV, clipping by MS or conservative (all procedures being performed by senior endovascular or vascular neurosurgeons); and 5) appropriate informed consent of patients and relatives according to criteria established by the Regional Ethics Committee. The exclusion criteria were: non-aneurysmal SAH, WFNS V, and history of psychiatric disorder or stroke.

Methodology

The clinical condition of each patient was graded according to the WFNS. Comorbidity was classified according to Charlson's scale (28). Based on CT scan, bleeding severity was classified according to Fisher's classification (29). Aneurysm locations comprised: anterior cerebral artery (ACA), internal cerebral artery (ICA) and middle cerebral artery (MCA); size was measured according to the largest saccular diameter. Outcome data were collected on interview by an independent nurse appointed by the hospital directorate of clinical research and investigations, at discharge and at 2, 6 and 12 months. The primary endpoint was modified Rankin Scale (mRS) (30), classifying patients as independent (mRS ≤ 2), dependent (mRS 3-5) or deceased (mRS 6). The causes of morbidity and mortality (mRS 3-6), determined by the principal investigators (FP, SB), were classified as: initial bleeding, rebleeding, procedural ischemia or hemorrhage, non-procedural ischemia, hydrocephalus, and medical (infectious, hyponatremia or cardiopathy). Functional assessment considered multiple additional outcome measures. Cognitive impairment was assessed on the mini-mental state examination (MMSE) as MMSE score was <23 (31, 32). Independence was assessed on the Activities of Daily Living Index (ADLI) scale [independence, score ≥ 4] (33) and the Lawton Instrumental Activities of Daily Living (IADL) scale [0 = dysautonomia to 8 = autonomy] (34). Quality of life (QoL) was evaluated on the international EORTC-QLQ-C30 questionnaire (35), scored on 30 items (version 3), including: global health status, 5 functional scales (physical, role, emotional, cognitive and social), 3 symptom scales (fatigue, nausea and vomiting, pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea). The scales and single-item measures (appendix) ranged from 0 to 100, higher scores corresponding to higher response levels: thus, a high score for global health status/QoL represented high QoL, a high score for a functional scale represented a high level of functioning, and a high score for a symptom scale or item represented a high level of symptomatology/problems.

Statistical analysis

Quantitative variables such as age were expressed as mean ± standard deviation, with two-group comparisons using Student's t-test. Categorical variables (gender, ratio, WFNS classification, Fisher's classification, topography and size of aneurysm, mRS and causes of unfavorable outcome) were expressed as proportions with 95% confidence intervals (95% CI), with comparison using Pearson's chi-squared test or Fisher's exact test as appropriate. P-value less than 0.05 were considered significant.

Results

Between November 2008 and October 2012, the 310 patients, included prospectively with mean time to admission after aneurysmal rupture of 1.9 ± 5 days [95% CI, 1.3-2.5], were treated as follows: EV for 208 (67.1%), MC for 54 (17.4%) and conservative treatment for 48 (15.5%).

Baseline characteristics of population

There was large female predominance in all 3 cohorts, but significant differences [F ratio = 34.2, p < 0.0001] in mean age, which was higher in the conservative treatment group (Table 1). The educational level differed little between the 3 cohorts, although the rate of higher education was greater in the EV and MS cohorts.

Mean Charlson score was significantly different between the 3 cohorts [F ratio = 4.15, p = 0.0016]: compared to the EV arm scores were higher in conservative arm and lower in the MS arm. Among vascular risk factors, only hypertension was distributed differently between arms [$\chi 2$ = 10.4, p = 0.0056].

SAH characteristics (WFNS and Fisher) were similar between the 3 arms. Aneurysm location differed, with predominance of anterior communicating artery aneurysms in the EV arm and predominance of MCA aneurysms in the MS arm [$\chi 2$ = 28.2, p <0.0001], while in the conservative arm the distribution of locations was that observed in the global population. All other aneurysm characteristics (diameter, neck size, multiple aneurysms) were similar in all 3 arms.

Independence, dependency and mortality

At discharge (Table 2), for the 252 patients WFNS score I-III at admission, the independence rate was 38.2% (n = 96), dependency rate 47.1% (n = 118), and mortality rate 14.7% (n = 37). For the 58 WFNS IV patients, rates were 3.4% (n = 2), 55.2% (n = 32) and 41.4% (n = 24), respectively.

At discharge, all causes (Table 3) of dependence and mortality were significantly more frequent in the conservative treatment cohort than in the other 2 (Pearson's χ^2 test, F ratio = 10.3; p = 0.0055). Procedural events were more frequent in the MS than in the EV cohort, due to a higher rate of ischemia (Fisher's exact test, odds ratio = 0.305 [95% CI, 0.09-1.01]; p = 0.02). The rate of post-procedural rebleeding was respectively 1.5% and 1.9% in the EV and

MS cohorts, but was responsible for a 25% morbidity and mortality rate (n = 12) in the conservative treatment cohort (in which 9 patients presented with WFNS I-III on admission).

In the first year following the aSAH (Table 2), independence improved regardless of clinical status at admission. At 12 months (41 patients lost to follow-up, 13.2%), the independence rate among the 252 patients admitted with WFNS I-III increased to 52.8% (n = 133), the dependence rate decreased to 13.2% (n = 33) and the mortality rate was to 22.2% (n = 56). Among the 58 patients admitted with WFNS IV, these rates were respectively 10.3% (n = 6), 10.3% (n = 6) and 60.4% (n = 58).

According to treatment procedure (EV, MS or conservative), the independence rates of patients admitted with WFNS I-III were 58.9%, 50% and 12.1% respectively, while the dependence rate was similar in the 3 arms: respectively, 11%, 19.6% and 18.2% (Figure 1). Thus, curative treatment (EV and MS) decreased mortality without increasing dependence. On the other hand, in WFNS IV patients, MS treatment increased dependence, at 37.5%, compared with the other 2 arms.

Functional outcome at 1 year

At 1 year, MMSE (Table 4) was administered to 116 (83.5%) of the 139 independent patients, and 30 (76.9%) of the 39 dependent patients. The test revealed pathological findings (<23) in 18 (15.5%) of the independent and 22 (73.3%) of the dependent patients. Analyzing the group of independent patients according to occlusion procedure, MMSE scores were pathological in 14 (14.9%) of the 94 EV patients, 4 (21.1%) of the 19 MS patients and none of the 3 managed conservatively, without significant difference. In the total population (regardless of independence), MMSE score was pathological in 26 (23.2%) of the 112 EV patients, 10 (40%) of the 25 MS patients and 4 (44%) of the 9 treated conservatively, without significant difference [Pearson's χ^2 test, F ratio = 4.29; p = 0.11].

Mean autonomy scores in the whole evaluated cohort were 5.2 ± 0.1 for ADLI and 6.1 ± 0.2 for IADL (Table 4). According to occlusion procedure, ADLI and IADL scores significantly differed between MS (respectively: 4.7 ± 0.3, p <0.01; 5.5 ± 0.4, p <0.05) and conservative treatment (respectively: 4.2 ± 0.4, p <0.002; 3.6 ± 0.7, p <0.0001).

Regarding QoL (Table 4), overall score was similar between the EV and MS cohorts, but significantly lower in the conservative treatment cohort, and the same held for the physical, cognitive and social functioning scores. Emotional functioning was significantly lower in the MS and conservative treatment cohorts.

Regarding symptoms and items, fatigue scores, nausea, dyspnea and loss of appetite were significantly frequent in the conservative treatment cohort. Insomnia was significantly more common in the MS cohort. Financial difficulties mainly concerned the conservative treatment cohort.

Discussion

Analysis of the 310 patients in the FASHE trial revealed that 58.9%, 50% and 12.1% of the patients aged 70 years and over admitted with WFNS I-III following aSAH had undergone EV, MS and conservative treatment, respectively. For patients with WFNS IV-V on admission, MS treatment was associated with 37.5% dependence. Cognitive outcome was similar in all 3 arms, while independence and QoL were mainly impaired in patients in the conservative treatment cohort.

Conservative treatment has long been an ethically sound option for the management of elderly patients with aSAH, given the expected poor functional prognosis. According to the literature, this strategy entails low independence and high mortality (14, 36), nonetheless previous studies failed to identifying the exact causes for this poor outcome. The present series confirmed these results: rates of dependence and of mortality for patients with WFNS I-III at admission were 18.2% and 63.6% respectively; however, the study was able to establish direct causality. The causes of dependence and mortality were dominated by initial SAH (37.5%), followed by rebleeding in 12 patients (25%) despite good initial clinical status (WFNS I-III) in 9 of them. The rebleeding rate in the literature was 15% for elderly patients treated with SAH without occluding the ruptured aneurysm (17, 37). Thus, in elderly patients with conservative treatment, rebleeding is the major cause of morbidity and mortality. Interventional treatment, whether EV or MS, is indispensable for patients in good clinical condition on admission, regardless of the severity of the associated comorbidities.

However, recent retrospective series of EV and MS reported favorable progression in 25-60% of patients, and a significant reduction of mortality (6, 10, 11, 14, 16, 21, 38, 39). The present prospective series showed that, after EV or MS treatment, patients with good initial clinical status (WFNS I-III) not only had relatively low mortality (between 15% and 18%); more importantly, the proportion of dependent patients was identical to that in younger patients. In contrast, in patients admitted with WFNS IV, the dependency rate was higher after MS (37.5%) compared to the EV group. This finding is to be considered with caution, as the sample was small and the surgery was for patients with cerebral hemorrhage. Overall, interventional treatments significantly decrease mortality without increasing dependence, or the socio-economic cost of caring for these elderly patients.

During the last two decades, the ISAT study confirmed the interest of endovascular procedures in the treatment of cerebral aneurysm (2, 5, 40, 41). The present prospective study confirmed the predominance of EV treatment in France: 67.1% of patients were treated using this procedure, despite inclusion in FASHE by teams composed of vascular neurosurgeons (16). This raises questions as to the current role of MS in this age group, in agreement with Smith et al. (21) in their broad review of retrospective series published between 1995 and 2008, reporting more favorable results after EV occlusion than MS clipping of ruptured and unruptured intracranial aneurysms in elderly subjects. However, these results from a nonexhaustive analysis of retrospective series were not reinforced by randomized controlled studies comparing the 2 interventional procedures (coiling vs clipping) in the elderly. Rittleford et al. (6) compared 128 EV vs. 140 MS procedures, and reported that clinical progression was significantly more favorable after EV treatment for ICA aneurysm, and after MS clipping for MCA aneurysm. Proust et al. (26), in the randomized stage of the FASHE trial, compared 2 groups of 20 patients 1 year after aneurysm rupture and did not observe any significant difference in the rate of independence. In the EV and MS cohorts prospectively reported in the present study, choice of treatment was based on a multidisciplinary discussion, and rates of independence, dependence and mortality were similar. Thus, in case of optimized treatment, MS clipping still has a role, because there are situations of high risk of post-EV ischemia in the elderly subjects: difficult EV navigation due to arterial sinuosity or atherosclerosis in large arteries or complex aneurysmal sac obliges the neuroradiology team to associate complementary techniques to coiling, such as stenting or remodeling.

To our knowledge, prospective evaluation of cognition, daily living activities and QoL in the elderly population after ruptured intracranial aneurism is rare. The only noteworthy study was a recent meta-analysis by Smith et al. that assessed QoL using formulas that converted mRS or GOS scores from retrospective series of elderly patients (21). They concluded that QoL was better preserved after EV than MS treatment regardless of whether the aneurysm was ruptured or unruptured. This extrapolation from the literature must be compared with the present prospective data. The MMSE is a comprehensive cognition test that is easy to implement, fast, robust and adapted to stroke monitoring (32). In longitudinal studies, 40% to 60% of elderly patients with aSAH had normal cognition (MMSE score $\geq$ 27) in the long term (42-45). Dichotomizing patients by age (> 45 vs. $\leq$45), Gupta et al. found greater cognitive impairment in subjects > 45 years of age (45). Bearing in mind that only 80% of the present patients were evaluated at 1-year, it is important to note that the cognitive impairment rate

(MMSE score <23) in independent patients was between 15% and 20% regardless of treatment procedure. These findings reinforce the usefulness of occlusion of ruptured aneurysm even in elderly patients, as cognitive impairment was no greater than with conservative treatment. Dysautonomia (ADLI and IADL scores) affecting personal hygiene care and also external relations was significantly worse in the MS than in the EV cohort and worse again in the conservative treatment cohort. QoL was generally preserved, with no difference between the EV and MS cohorts, except for emotional functioning and the prevalence of insomnia. In contrast, conservative treatment resulted in significant impairment of QoL compared with the interventional arms. Finally, interventional management of ruptured aneurysm in patients over 70 years of age resulted in better preservation of cognitive functions, autonomy and QoL.

The limitations of this prospective multicenter study lay in the clinical differences between the 3 treatment cohorts: the conservative treatment cohort had higher average age and comorbidity score than the other two. Each participating team was free to propose the procedure that seemed the most appropriate. Logically, the distribution of patients was governed by multiple factors: conservative treatment was rarely proposed to patients in good clinical condition at admission (and, as noted above, the mean age and comorbidity score of this group were significantly higher than in EV and MS); MS treatment mainly involved patients with MCA aneurysm, and a majority of patients overall received EV coiling. Given the physiological loss to follow up, functional analysis at 1 year involved only part of the initial population: 146 (47.1%) of the overall cohort for MMSE, 169 (54.5%) for ADLI, and 149 (48.1%) for QoL. The main strong point of our study is that it was the only trial on cognition and QOL after aSAH conducted in such a large sample of patients over 70 years of age; moreover, questionnaires were not self-administered but filled out by specialized research department staff, assisting patients and their relatives. In addition, the neurovascular team responsible for initial patient care was not involved in this later functional assessment. This is particularly important because, when there is risk of inclusion bias, biases in analysis, data collection and long-term evaluation are reduced by independent investigation and quality control throughout the trial.

Conclusion

Any ruptured cerebral aneurysm in an elderly patient in good clinical condition at admission should be treated, regardless of the weight of associated comorbidities. On the other hand, patients admitted for severe forms of aSAH should be the object of thorough discussion between the multidisciplinary team and relatives of the patient, because interventional treatment, whether EV or MS, incurs an increased rate of dependence. At 1 year after interventional management of ruptured aneurysm in patients with good initial baseline, cognition, autonomy and QoL were preserved similarly, whichever the occlusion procedure. These results are a useful contribution to the arguments in favor of extending interventional management of aSAH in the elderly population.

Contributors Statement

Primary authorship was the responsibility of F. Proust and S. Bracard. J. Bénichou was responsible for all statistical aspects and analysis. K. Lallouche was responsible for data analysis, editing, preparation of Tables and verification.
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Disclosures

None

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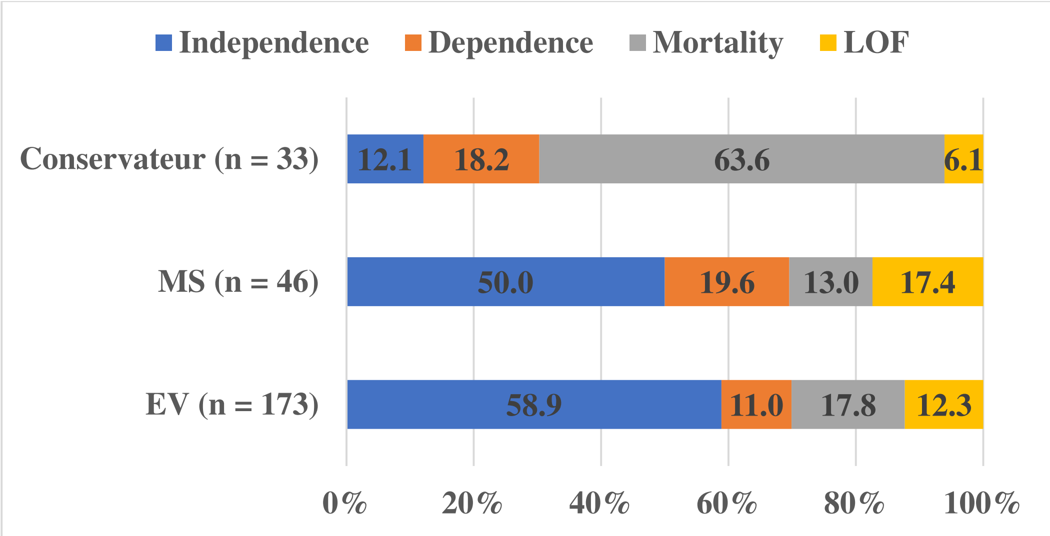
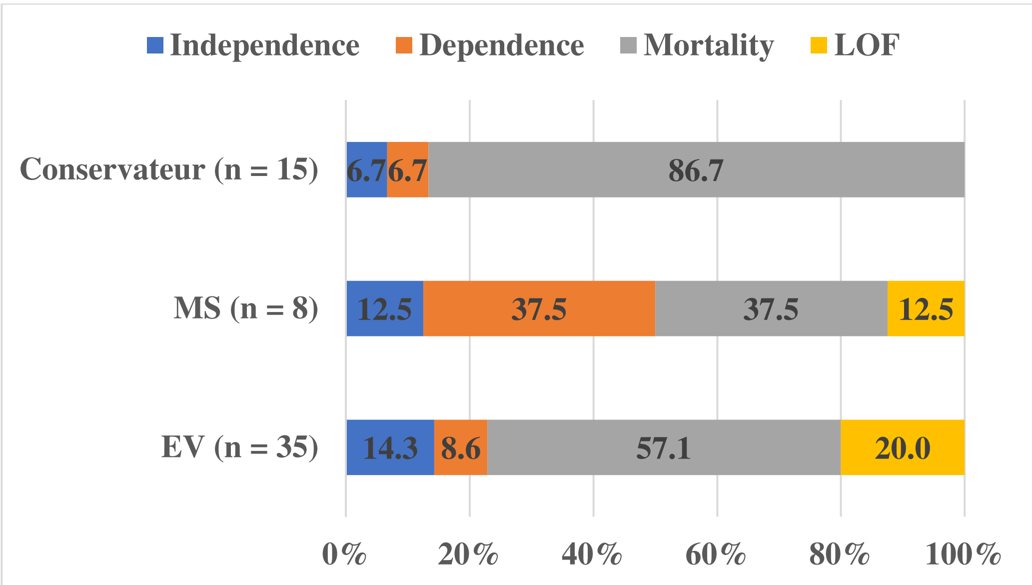
Figure 1. At 12 months, ratios of independence, dependence and mortality according to endovascular occlusion (EV), microsurgical clipping (MS) or conservative approach.

A. WFNS I-III.



B. WFNS IV.



Legends. Cons., conservative; EV, endovascular; LOF, loss of follow-up; MS, microsurgical; WFNS, world federation of neurological surgeons.

Table 1. Baseline characteristics of elderly patients (≥ 70 years old) with ruptured IA (n = 310).

Variables	Endovascular (EV) n = 208 (67.1%) [95% CI]	Microsurgical (MS) n = 54 (17.4%) [95% CI]	Conservative n = 48 (15.5%) [95% CI]	Total n = 310 (100%) [95% CI]
Sex ratio F/M	4.2 (168/40)	8 (48/6)	7 (42/6)	4.9 (258/52)
Age (years) *	77.2 ± 4.7 [76.5-77.8]	76.1 ± 3.9 [75-77.1]	82.9 ± 5.3 [81.4-84.5]	77.9 ± 5.1 [77.3-78.4]
Educational level				
Primary school	63 (30.3)	19 (35.2)	24 (50)	106 (34.2)
Secondary school	73 (35.1)	18 (33.3)	17 (35.4)	108 (34.8)
Vocational training	18 (8.7)	10 (18.5)	2 (4.2)	30 (9.7)
University	25 (12)	5 (9.3)	1 (2.1)	31 (10)
NA	29 (13.9)	2 (3.7)	4 (8.3)	35 (11.3)
Charlson score † (comorbidity)	4 ± 1.4 [3.8-4.2]	3.7 ± 1.2 [3.4-4]	4.5 ± 1.2 [4.1-4.9]	4 ± 1.4 [3.9-4.2]
Vascular risk factors				
Smoking 1	143 (68.8)	47 (87)	37 (77.1)	227 (73.2)
Smoking 2/3	51 (24.5)/12 (5.8)	5 (9.3)/2 (3.7)	10 (20.8)/1 (2.1)	66 (21.3)/15 (4.8)
Cholest. > 5 mmol/l	48 (20.4)	11 (20)	13 (27.1)	72 (23.3)
HT, diast. > 90 mmHg ‡	79 (34.7)	43 (57.3)	27 (56.3)	149 (42.5)
Alcohol, > 3 glasses/d.	6 (2.9)	2 (3.7)	0 (0)	8 (2.6)
WFNS classification				
WFNS I (GCS 15)	96 (46.2)	21 (38.9)	12 (25)	129 (41.6)
WFNS II (GCS 13-14)	61 (29.3)	18 (33.3)	16 (33.3)	95 (30.7)
WFNS III (deficit)	16 (7.7)	7 (13)	5 (10.4)	28 (9)
WFNS IV (GCS 7-12)	35 (16.8)	8 (14.8)	15 (31.3)	58 (18.7)
SAH on CT scan				
Fisher 0	3 (1.4)	1 (1.9)	1 (2)	5 (1.6)
Fisher 1	21 (10.1)	3 (5.5)	3 (6.1)	27 (8.7)
Fisher 2	51 (24.5)	8 (14.8)	6 (12.5)	65 (21)
Fisher 3	96 (46.2)	25 (46.3)	27 (56.5)	148 (47.7)
Fisher 4	37 (17.8)	17 (31.5)	11 (22.9)	65 (21)
Ruptured IA location §				
ACA	102 (49.1)	11 (20.4)	23 (48)	136 (43.9)
MCA	21 (10.1)	32 (59.3)	10 (20.8)	63 (20.3)
ICA	61 (29.3)	9 (16.7)	10 (20.8)	80 (25.8)
VBA	24 (11.5)	2 (3.6)	5 (10.4)	31 (10)
Ruptured IA size				
Diameter	7.3 ± 6.6 [6.4-8.2]	6.7 ± 5.5 [5.1-8.2]	7.6 ± 6.3 [5.7-9.4]	7.2 ± 6.4 [6.5-8]
Neck ≤ 4 mm	153 (74.6)	37 (68.5)	29 (60.4)	219 (71.3)
Multiple IA	40 (19.9)	8 (15.1)	5 (10.6)	53 (17.6)

Legends. ACA, anterior cerebral artery; Cholest., total cholesterol; diast., diastolic; IA, intracranial aneurysm; CI, confidence interval; ICA, internal carotid artery; GCS, Glasgow coma scale; HT, hypertension (diastolic > 90 mmHg); MCA, middle cerebral artery; Smoking 1: never smoking, 2: occasional smoking, 3: > 5 cigarettes/day; VBA, vertebrobasilar artery; WFNS, World Federation of Neurological Surgeons.
* Significant difference in mean age between the 3 cohorts [F ratio = 34.2, $p < 0.0001$].
† Significant difference in Charlson score between the 3 cohorts [F ratio = 4.15, p = 0.0016].
‡ Significant difference in HT between the 3 cohorts [$\chi^2 = 10.4$, p = 0.0056].
§ Significant difference in aneurysm location between the 3 cohorts [$\chi^2 = 28.2$, $p < 0.0001$].

Table 2. Outcome of elderly patients (≥ 70 years old) with ruptured IA (n = 310), according to mRS score.

Outcome	***Discharge n (%)***		***2 months n (%)***		***6 months n (%)***		***12 months n (%)***	
WFNS	***I-III***	***IV***	***I-III***	***IV***	***I-III***	***IV***	***I-III***	***IV***
Lost to follow-up	***1 (0.2)***	***0***	***11 (4.4)***	***2 (2.9)***	***19 (7.5)***	***6 (10.3)***	***30 (11.8)***	***11 (19)***
No data	***0***	***0***	***8 (3.2)***	***1 (1.5)***	***13 (5.1)***	***1 (1.8)***	***0***	***0***
mRS 0	18 (7.2)	0	38 (15.1)	1 (1.7)	50 (19.8)	0 (0)	60 (23.8)	2 (3.5)
mRS 1	38 (15.1)	1 (1.7)	49 (19.4)	0 (0)	48 (19.1)	5 (8.6)	48 (19.1)	4 (6.9)
mRS 2	40 (15.9)	1 (1.7)	38 (15.1)	4 (6)	31 (12.3)	2 (3.4)	25 (9.9)	0 (0)
mRS 0-2 (Independent)	***96 (38.2)***	***2 (3.4)***	***125 (49.6)***	***5 (7.7)***	***129 (51.2)***	***7 (12)***	***133 (52.8)***	***6 (10.3)***
mRS 3	57 (22.7)	9 (15.5)	24 (9.5)	8 (13.8)	19 (7.5)	3 (5.2)	17 (6.8)	4 (6.9)
mRS 4	34 (13.6)	11 (19)	22 (8.7)	8 (13.8)	14 (5.6)	3 (5.2)	12 (4.8)	0 (0)
mRS 5	27 (10.8)	12 (20.7)	22 (8.7)	5 (8.6)	6 (2.4)	5 (8.6)	4 (1.6)	2 (3.5)
mRS 3-5 (Dependent)	***118 (47.1)***	***32 (55.2)***	***68 (26.9)***	***21 (36.4)***	***39 (15.5)***	***11 (19)***	***33 (13.2)***	***6 (10.3)***
mRS 6 (Mortality)	***37 (14.7)***	***24 (41.4)***	***40 (15.9)***	***29 (50)***	***52 (20.7)***	***33 (56.9)***	***56 (22.2)***	***35 (60.4)***
Total	***252 (100)***	***58 (100)***	***252 (100)***	***58 (100)***	***252 (100)***	***58 (100)***	***252 (100)***	***58 (100)***

Key. IA, intracranial aneurysm; mRS, modified Rankin Score; WFNS, World Federation of Neurological Surgeons

Table 3. At discharge, causes of morbidity and mortality (mRS > 2) in 310 elderly patients (≥ 70 years) according to aneurysm treatment procedure.

Causes	**Endovascular n = 208 n (%)**	**Microsurgical n = 54 n (%)**	**Conservative n = 48 n (%)**
SAH *	40 (19.2)	7 (13)	18 (37.5)
Procedural events			
Hemorr.	1 (0.5)	1 (1.9)	
Ischemia	9 (4.3)	7 (13)	
Post-procedural rebleeding	3 (1.5)	1 (1.9)	12 (25)
Non-procedural ischemia	34 (16.3)	12 (22.1)	5 (10.4)
Hydrocephalus	28 (13.5)	4 (7.2)	3 (6.3)
Infection			
Lung	13 (6.3)	1 (1.9)	5 (10.4)
Ventriculitis	1 (0.5)		
Other	2 (1)		
Hyponatremia	1 (0.5)		
Cardiopathy	1 (0.5)		1 (2.1)
TOTAL	134 (64.1)	33 (61.1)	44 (91.7)

Legends. Hemorr., hemorrhagic; SAH, subarachnoid hemorrhage.
*, Significant difference in SAH ratio between the 3 cohorts [Pearson's χ^2 test, F ratio = 10.3, p = 0.0055].

Table 5. At 12 months, functional outcome according to treatment procedure in elderly patients (≥ 70 years) with aneurysmal SAH.

Functional outcome	Endovascular (n = 208) n Mean± SD [95%CI] (%)	Microsurgical (n = 54) n Mean ± SD [95%CI]	p MS versus EV	Conservative (n = 48) n Mean ± SD [95%CI]	p Conservative versus EV	TOTAL (n = 310) n Mean ± SD [95%CI]
Mini-Mental State (/ 30)	n = 112 (49.1)	n = 25 (46.3)		n = 9 (18.8)		n = 146 (47.1)
Mean ± SD [95%CI]	25 ± 0.6 [23.7-26.2]	23.4 ± 1.3 [20.7-26.1]	0.3	21.6 ± 2.3 [17.1-26]	0.11	24.5 ± 0.6 [23.4-25.6]
Impaired (score < 23)	26 (23.2)	10 (40)		4 (44)		40 (27.4)
Activities of Daily Living Index (ADLI / 6)	n = 125 5.4 ± 0.1 [5.2-5.73]	n = 32 4.7 ± 0.3 [4.2-5.3]	0.01	n = 12 4.2 ± 0.4 [3.3-5.1]	0.002	n = 169 (54.5) 5.2 ± 0.1 [5-5.4]
Instrumental Activities of Daily Living (IADL / 8)	n = 124 6.5 ± 0.2 [6-6.9]	n = 31 5.5 ± 0.4 [4.6-6.4]	0.05	n = 12 3.6 ± 0.7 [2.1-5]	0.0001	n = 167 (53.9%) 6.1 ± 0.2 [5.7-6.5]
Quality of Life / 100	n = 111	n = 28		n = 10		n = 149 (48.1)
Global health status / QOL						
Global health status / QOL	71.2 ± 2.4 [66.4-75.9]	65.8 ± 4.6 [56.5-75.1]	0.3	53.3 ± 8 [37.4-69.3]	0.03	68.9 ± 2.1 [64.8-73.1]
Functional scales						
Physical functioning	77.3 ± 2.6 [72.1-82.4]	74.5 ± 5 [64.2-84.8]	0.6	37.3 ± 8.7 [20.1-54.5]	< 0.0001	74 ± 2.3 [69.3-78.8]
Role functioning	79.7 ± 3.1 [73.4-85.1]	73.2 ± 6.3 [60.6-85.8]	0.3	36.7 ± 10.6 [15.6-57.7]	0.001	75.6 ± 2.8 [69.9-81.3]
Emotional functioning	82.5 ± 2.1 [78.1-86.5]	69.3 ± 4.2 [61-77.6]	0.006	62.5 ± 7 [48.6-76.4]	0.003	78.6 ± 1.8 [74.8-82.3]
Cognitive functioning	79.3 ± 3.2 [72.8-85.7]	72.6 ± 6.4 [59.9-85.4]	0.3	90 ± 11 [68.7-111.3]	0.3	78.7 ± 2.7 [73.2-84.2]
Social functioning	84.5 ± 2.8 [78.8-90.2]	77.4 ± 5.7 [66.1-88.6]	0.2	46.7 ± 9.5 [27.8-65.5]	0.0001	80.6 ± 2.5 [75.6-85.7]
Symptom scales						
Fatigue	26.1 ± 2.5 [19.6-29.7]	30.2 ± 5.1 [20.1-40.2]	0.3	50 ± 8.5 [33.2-66.8]	0.003	27.4 ± 2.3 [22.9-31.8]
Nausea, vomiting	21.3 ± 2.2 [16.9-25.8]	27.4 ± 4.5 [18.5-36.2]	0.2	41.7 ± 7.5 [26.9-56.4]	0.005	23.8 ± 1.9 [19.9-27.7]
Pain	15.9 ± 2.3 [11.5-20.4]	23.8 ± 4.5 [14.9-32.7]	0.1	20 ± 7.5 [5.1-34.9]	0.5	17.7 ± 2 [13.8-21.5]
Single items						
Dyspnea	11.7 ± 2.1 [7.5-15.9]	11.9 ± 4.3 [3.5-20.3]	0.9	30 ± 7.1 [15.9-44.1]	0.01	13 ± 1.8 [9.3-16.7]
Insomnia	18.3 ± 2.8 [12.6-24.1]	32.1 ± 5.7 [20.8-43.5]	0.03	30 ± 9.6 [11-48.9]	0.2	21.7 ± 2.5 [16.7-26.7]
Appetite loss	9.3 ± 2.2 [4.8-13.8]	15.5 ± 4.5 [6.6-24.4]	0.2	26.7 ± 7.5 [11.7-41.6]	0.01	11.6 ± 1.9 [7.7-15.5]
Constipation	13.2 ± 2.4 [8.4-17.9]	14.3 ± 4.8 [4.8-23.8]	0.8	23.3 ± 8.1 [7.3-39.3]	0.2	14.1 ± 2.1 [10-18.2]
Diarrhoea	3.3 ± 1.2 [0.8-5.8]	2.3 ± 2.5 [-2.6-7.4]	0.7	6.7 ± 4.2 [-1.6-15]	0.4	3.4 ± 1.1 [1.2-5.5]
Financial difficulties	1.8 ± 1.5 [-1-4.7]	7.1 ± 3 [1.3-13]	0.1	10 ± 5 [0.2-19.8]	0.004	3.3 ± 1.3 [0.8-5.9]

Legends. CI, confidence interval. QOL, quality of life (global evaluation by visual analogue scale (VAS)). SD, standard deviation.
p calculated using non-parametric Dunn's test, endovascular cohort as reference.