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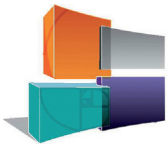

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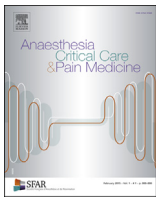

Original Article

Evolution of neurological recovery during the first year after subarachnoid haemorrhage in a French university centre

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ABSTRACT

Introduction: The evolution of neurological recovery during the first year after aneurysmal Subarachnoid Haemorrhage (SAH) is poorly described.
Patients: Patients with SAH in one university hospital from March the 1st 2010, to December 31st 2012, with a one-year follow-up.
Method: Evaluation was performed via phone call at 3, 6 and 12 months. Primary endpoint was poor neurological recovery (modified Rankin Scale 3–4–5–6), one year after SAH. Secondary endpoints were the incidence of lack of self-perceived previous health status recovery and incidence of cognitive disorders, one year after SAH. Risk factors of poor neurological recovery were retrieved with multivariable logistic regression.
Results: Two hundred and eleven patients were included and 208 had a complete follow-up. One hundred and twenty (57.7%) patients were female, 112 (53.8%) had a WFNS grade I–II–III. Seventy (33.6%) patients displayed one-year poor neurological outcome and risk factors of poor outcome were age, baseline Glasgow Coma Score $\leq$ 8, external ventricular drainage, intra-cranial hypertension and angiographic vasospasm. We observed an improvement in good outcome at 3 months [112 (53.8%) patients], 6 months [127 (61.1%) patients] and one-year [138 (66.3%) patients]. Fifty-nine (35.3%) patients recovered previous health status, 96 (57.5%) had persistent behaviour disorders, and 71 (42.5%) suffered from memory losses at one year.
Discussion: Neurological recovery seems to improve over time. The same key complications should be targeted worldwide in SAH patients.

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Conclusion: Neurological complications in the following of SAH should be actively treated in order to improve outcome. The early neuro-ICU phase remains a key determinant of long-term recovery.

1. Introduction

Aneurysmal subarachnoid haemorrhage (SAH) occurs in young healthy individuals and is a devastating form of stroke. Its incidence varies across countries and is around 9 case/100,000 inhabitants per year in France [1]. In spite of recent advances in the endovascular treatment of aneurysm and neurocritical care, the mortality rate remains high in SAH patients [2]. Survivors also experience severe neurological troubles: cognitive impairment, memory loss, mood disorders, speech disorders, etc. [3]. These troubles impair short and long-term quality of life, and 40 to 60% patients do not recover their previous work, which drastically impacts health-care costs [4,5]. The assessment of health-related status is thus a challenge that must take into account physical, psychological and social aspects which usual neurological scales (Rankin, Glasgow Outcome Scale for instance) do not extensively assess [6]. There are many studies reported factors predictive on functional outcome, but French cohorts have been little described so far.

The primary objective of our study was to evaluate the prognostic factors associated with poor neurological recovery one year after the onset of SAH, evaluated with the modified Rankin Scale [mRS] in a single-centre in France. The secondary objectives were to evaluate self-perceived health status recovery, the evolution of the mRS at different time-points (3, 6 and 12 months), other cognitive impairments during the first year after SAH, which are inadequately explored with the mRS.

2. Patients and methods

This was an observational study, performed according to STROBE guidelines (Appendix) [5] including all patients referred for the treatment of SAH in a French tertiary-care university hospital (Centre Hospitalier Universitaire de Nantes) from March the 1st 2010, to December 31st 2012. This study was approved by the local ethics committee (*Groupe Nantais d'Ethique dans le Domaine de la Santé*). Since the study was purely observational, consent was waived but patients received information, or their next-of-kin whenever the patient's state was not compatible with information.

2.1. Inclusion criteria

All adult patients admitted in our hospital for SAH confirmed by cerebral computed tomography (CT) were included. Exclusion criteria were traumatic subarachnoid haemorrhage, mycotic aneurysm, arteriovenous malformation or non-aneurysmal subarachnoid haemorrhage and patients with clinical signs of brain death at hospital admission, patients < 18 years and pregnant patients. Patients with a second episode of SAH during the follow-up period were not included.

2.2. Management protocol

The choice of treatment (clipping, coiling) was discussed between the neurosurgeon and interventional neuro-radiologist. Before aneurysm obliteration, systolic blood pressure was kept < 160 mmHg [7]. Aneurysm obliteration was performed in first 24 hours after hospital admission. In case of hydrocephalus, an external ventricular drain was placed. Intra-cranial haematoma evacuation and decompressive craniectomy were discussed if necessary. After obliteration (surgical or coiling) a systematic brain CT-scan was performed.

Patients were hospitalised in intensive care unit (ICU) in case of a World Federation of Neurosurgery (WFNS) Score $\geq$ III or in case of complications. Patients were sedated and underwent mechanical ventilation if Glasgow Coma Scale (GCS) was ≤ 8. Sedation protocol associated midazolam (0.2 to 0.5 $mg/kg^{-1}/h^{-1}$) and sufentanil (0.2 to 0.5 $mg/kg^{-1}/h^{-1}$). All patients were treated according to international guidelines [8]. Cerebral perfusion pressure (CPP) goal was between 60 and 70 mmHg after obliteration [9]. Intra-cranial hypertension was defined as an intra-cranial pressure $\geq$ 20 mmHg during 15 minutes [9]. When control of intra-cranial hypertension was poor, midazolam infusion was discontinued and barbiturate (sodium thiopental) was used (loading dose of 2–3 mg/kg^{-1}) followed by a continuous infusion (started dose of 2–3 $mg/kg^{-1}/h^{-1}$) adapted to the intra-cranial pressure evolution and bispectal index [10]. In case of refractory intra-cranial hypertension, therapeutic hypothermia and decompressive craniectomy were discussed during multi-disciplinary staff [11].

In order to prevent secondary brain damages, the therapeutic goals were: $PaO_2 \geq 80$ mmHg, $PaCO_2$ between 35 and 45 mmHg, natremia $\geq$ 135mEq/L, haemoglobin ≥ 8 g/dL^{-1}, glycaemia between 6 and 9 $mmol.L^{-1}$ and temperature between 36 °C and 38 °C [12]. Nimodipine was administered orally as soon as possible, from admission to day 21 [8]. Cerebral arteries velocities were recorded daily using trans-cranial Doppler ultrasonography in order to screen vasospasm [13].

Vasospasm was defined as narrowing of the arterial vessel lumen diagnosed with cerebral angiography or cerebral angiographic-CT scan [14]. The diagnosis was left at the neuro-radiologist discretion. Vasospasm treatment consisted in the association of normovolaemia and mean arterial pressure $\geq$ 100 mmHg [15]. Endovascular procedures consisted of mechanical or chemical angioplasty (nimodipine, milrinone in-situ) when assessed by expert neuro-radiologist [16]. Delayed cerebral ischemia (DCI) was defined by cerebral infarction on CT or magnetic resonance imaging within 6 weeks after SAH, not present between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment, according to international definitions [17]. Withdrawal of life support therapies were performed in agreement with multi-disciplinary medical and paramedical teams involved in patient's care, in accordance with French laws.

2.3. Data collection

Baselines demographics data included gender, age, history of hypertension, coronary disease, diabetes, Body Mass Index (BMI) > 30 kg/m^{-2}, alcohol abuse (> 30 grams per day), family history of aneurysmal SAH (at least 1 first-degree family member with an aneurysmal SAH). Localisation of the aneurysm, in-hospital complications including DCI, angiographic vasospasm, intra-cranial hypertension, barbiturate sedation, hydrocephalus, hyponatremia, seizures, septic shock, ventilator-acquired pneu-

monia [18], acute respiratory distress syndrome (ARDS) were listed. Duration of mechanical ventilation, hospital and intensive care length of stay were registered.

The outcome was assessed by phone call to the patient [19], family or caregivers for severely disabled patients, repeatedly after 3, 6 and 12 months after the SAH onset. A 40 minutes pre-planned telephone questionnaire was performed in each patient. One intensivist performed phone calls to limit inter-observer variability (JB.P.). In this questionnaire, neurological and quality-of-life recovery were assessed with the following: mRS version adapted to telephone exchanges [19], self-perceived previous recovery health status, perceived by the patient, self-perceived memory, speech disorders, behaviour or sleep disorders, resume of personal daily activities and resume to previous work [3]. All the latest items were declarative. In case the patient was unable to sustain a 40 minutes phone call interview, the evaluation was realised with the patient's next-of-kin or health-care professional.

2.4. Primary outcome

The primary outcome of the study was the neurologic recovery assessed with the modified Rankin Scale (mRS). Good neurologic recovery was defined as an mRS Score of 0–1–2 and poor neurologic recovery as a mRS Score of 3–4–5–6 [20]. We aimed at describing the risk factors of poor neurologic recovery at one-year.

2.5. Secondary outcomes

We studied the evolution of neurological recovery at the different time-points (mRS at 3, 6 and 12 months after SAH).

Since mRS is not designed to evaluate patient's global health status, we asked during each phone interview, whether the patient felt if he or she had recovered their previous health status at 3, 6 and 12 months.

Also, we planned to evaluate the incidence of cognitive dysfunctions and their evolution over time, which are not detailed in the mRS. Thus, we evaluated at 3, 6 and 12 months, the incidence of mood disorders, speech disorders, memory losses, sleep disorders, behaviour disorders. We also evaluated if patients could resume their previous job or daily activities during the same time frame.

Finally, one of the goals of this study was to detail the causes of morbidity during the in-hospital course after SAH in our institution: metabolic troubles, incidence of ventilator-acquired pneumonia, ICU hospitalisation, ICU length of stay, use of mechanical ventilation, use of vasopressor, occurrence of stress cardiomyopathy, dysnatremia...

2.6. Statistical analysis

Descriptive data were reported as mean ± standard deviation for continuous variables and as N (%) for categorical variables. Association between baseline characteristics, in-hospital complications, clinical/radiological variables, out of hospital status and absence of previous health condition recovery as a binary outcome were assessed using a univariate logistic regression analysis. Any variable associated with recovery outcome with a P-value ≤ 0.2 on univariate analysis was entered in a backward stepwise model using multivariate logistic regression analysis. The best model was selected according to the best Akaike Information Criterion and the parsimonious rule. A P-value of 0.05 or less was considered statistically significant in the final model.

A multivariate analysis model was performed for the primary outcome, defined as the classical definition based on the 12-months mRS. For this analysis, good neurological recovery was defined with a mRS Score of 0–1–2 [20] and poor neurological recovery with a mRS Score 3–4–5–6. Because, mRS is not designed to evaluate health status in its entirety, and also because recovery of previous health status is of primary concern to patients and relatives, we also elaborated a multivariate model about the potential factors associated with the lack of self-perceived previous health recovery, assessed by the patients during phone call.

Recent randomised-controlled studies [20] displayed 26% of poor neurological outcome in subarachnoid haemorrhage patients. We decided to include 200 patients with a complete follow-up, in order to include at least 50 patients with a poor outcome, in order to perform a multivariable analysis with at least 5 risk factors. Patients with incomplete follow-up were not kept in the analysis.

Statistical analyses were performed with R studio®, v 1.01.136, and with SAS JMP13® (SAS Corporation®, Cary, North Carolina, United States) softwares.

3. Results

3.1. Characteristics

Two hundred and eleven patients were included and 208 had complete follow-up during the study period. One hundred and twenty (57.7%) were female, the median age was 55 years [45–65] and 75 (36.1%) patients suffered from hypertension. On admission 112 (53.8%) had WFNS grade I-II-III and 133 (63.9%) patients had a Fisher grade 4. One hundred and eighty-four (89%) were treated with endovascular coils embolization, 20 (9%) patients had their aneurysm surgically clipped and external ventricular drainage was necessary in 104 patients (50%). Admission in the intensive care unit (ICU) was required in 181 (87%) patients. Complete baseline characteristics are presented in Table 1.

During hospital course, DCI was diagnosed in 69 (33.2%) patients, angiographic vasospasms in 53 (25.5%) and intracranial hypertension in 61 (29.3%). Eighty-six (41.3%) patients developed

Table 1
Baseline characteristics of patients hospitalised for SAH in a single French university centre.

	Good neurological recovery N = 138	Poor neurological recovery N = 70	P
Age	52.5 (44–63.8)	60 [51.2–70]	< 0.001
Sex (Female)	80 (58)	40 (57.1)	
BMI > 30	16 (11.6)	8 (11.4)	
GCS at admission	14 (11–15)	6 (4–10)	< 0.0001
WFNS grade			< 0.001
I	62 (44.9)	3 (4.3)	
II	29 (21.0)	5 (7.1)	
III	11 (8.0)	2 (2.9)	
IV	19 (13.8)	22 (31.4)	
V	17 (12.3)	38 (54.3)	
Fisher grade			< 0.001
I	6 (4.3)	0	
II	36 (26.1)	1 (1.4)	
III	23 (16.7)	9 (12.9)	
IV	73 (52.9)	60 (85.7)	
Hypertension	45 (32.6)	30 (42.9)	
Diabetes	6 (4.3)	5 (7.1)	
Alcohol consumption	16 (11.6)	12 (17.1)	
Chronic medication			
Beta-blockers	11 (8)	11 (15.7)	
Aspirin/clopidogrel	10 (7.2)	10 (14.3)	
Vitamin K agonists	4 (2.9)	4 (5.7)	

Good recovery was defined with a modified Rankin Scale = 0–1–2, 12 months after the onset of SAH. Poor recovery was defined as mRS = 3–4–5–6, 12 months after the onset of SAH. GCS: Glasgow coma score; WFNS: world federation of neurosurgeons; BMI: body mass index.

Table 2
Neurologic complications and main in-hospital events.

	Good neurological recovery N = 138	Poor neurological recovery N = 70	*P*
Neurologic management			
External ventricular drainage	54 (39.1)	50 (71.4)	0.0003
Delayed cerebral ischemia	40 (29.0)	29 (41.4)	
Angiographic vasospasm	32 (23.2)	21 (30.0)	
Intracranial hypertension	21 (15.1)	40 (57.1)	
Decompressive craniectomy	3 (2.2)	7 (10.0)	0.02
Barbiturate coma	14 (10.1)	26 (37.1)	< 0.01
Seizures	20 (14.5)	15 (21.4)	
Use of anti-epileptic drugs	28 (20.3)	21 (30.0)	
In-hospital events			
Hyponatremia ($\leq$ 135 mmol.L^{-1})	53 (38.4)	17 (24.3)	
Chronic CSF shunting	13 (9.4)	13 (18.6)	< 0.002
Ventilator-acquired pneumonia	41 (29.7)	45 (64.3)	< 0.0001
Urinary tract infection	15 (10.9)	15 (21.4)	
Septic Shock	6 (4.3)	11 (15.7)	
ARDS	6 (4.3)	9 (12.9)	
Stress cardiomyopathy	11 (8.0)	9 (12.9)	
Number of patients under MV	69 (50.0)	65 (92.9)	< 0.00001
MV duration (d)	10 (2–19)	11 [3–35]	
ICU length of stay (d)	5 (1–15)	12.5 [5–40]	< 0.00001
Vasopressive drugs duration (d)	0 [0–4]	4 (2–6)	< 0.001
Withdrawal or withholding of life sustaining-therapies	0	22 (31.4)	<0.0001
Hospital length of stay (days)	19 [12–35]	26 [7–68]	

MV: mechanical ventilation $\geq$ 24 hours. Continuous data are expressed as mean (standard deviation) or median (interquartile). Categorical data are expressed as N (%). ARDS: acute respiratory distress syndrome; CSF: cerebro-spinal fluid; ICU: intensive care unit; NB: withdrawal of life-sustaining Therapies was not uphold in the regression model.

ventilator-acquired pneumonia. The median in hospital length of stay was 20 [11–45] days. Complete in-hospital complications are listed in Table 2.

3.2. Primary endpoint

Seventy patients (33.6%) displayed one-year poor neurological outcome. The risk factors associated with poor neurological recovery were: age (OR 1.1-IC$_{95}$ [1.02–1.11], $P < 0.001$), baseline GCS $\leq$ 8 (OR 1.32-IC$_{95}$ [1.22–2.18], $P < 0.01$), external ventricular drainage (2.12-IC$_{95}$ [1.08–6.22], $P < 0.05$), the occurrence of intra-cranial hypertension (12.55-IC$_{95}$ [4.84–36.39], $P = 0.001$), the presence of vasospasm (2.62-IC$_{95}$ [1.07–6.72], $P < 0.05$) (Table 3).

3.3. Secondary endpoints

Regarding the risk factors associated with the lack of previous self-perceived health status recovery, 12 months after the onset of SAH, we found: female sex (OR 2.28-IC$_{95}$ [1.19–4.28], $P = 0.01$), a low GCS on admission (GCS $\leq$ 8 OR 8.3-IC$_{95}$ [1.6–20], $P < 0.01$), the occurrence of intra-cranial hypertension (3.03-IC$_{95}$ [2.12–17.55], $P < 0.001$), the presence of vasospasm (2.56-IC$_{95}$ [1.24–5.48], $P < 0.001$) and the occurrence of a ventilator-acquired pneumonia (6.20-IC$_{95}$ [2.66–15.89], $P < 0.001$) (Table 4).

In the first year following SAH, we observed an improvement of the good neurologic outcome (mRS 0–1–2) with 112 (53.8%) patients at 3 months, 127 (61.1%) patients at 6-months and 138 (66.3%) patients at one-year (Fig. 1).

Regarding the cognitive dysfunctions at 12 months, 96 (57.5%) patients displayed behaviour disorders, 71 (42.5%) patients displayed memory losses, 41 (24.6%) patients displayed speech disorders. Only 62 (37.3%) patients could resume their previous work. The evolution during the first year after SAH of cognitive dysfunctions and quality-of-life is displayed in Table 5.

4. Discussion

This French monocentric cohort found that age, poor baseline GCS, intra-cranial hypertension, angiographic vasospasm and the presence of external ventricular drain were associated with a poor one-year neurological outcome. We observed a neurological improvement during the first year of follow-up.

This result challenges the usual 3-months evaluation of neurological recovery after SAH [20], since it is possible that this time-frame is too short after ICU admission to adequately assess neurological outcome. However, longer follow-up is time and resources-consuming and could lead to a lost in the follow-up. There are currently few SAH cohorts with systematic time-points evaluations [3]: there is usually one time-point [3,21] which is usually not standardised [3] and cohorts with long-term follow-up often could bear a modest number of patients [3]. Also, these studies usually provide descriptive data [3], the risk factors of poor

Table 3
Multivariate analysis of risk factors associated with poor one-year neurological outcome in a single centre cohort of 208 patients with SAH.

	Odds ratio	95% confidence of interval	*P*
Age	1.1	1–1.1	< 0.001
GCS $\leq$ 8	1.3	1.2–2.9	< 0.01
External ventricular drain	2.1	1.1–6.2	< 0.05
Intra-cranial hypertension	12.5	4.8–36.4	0.001
Vasospasm	2.6	1.1–6.7	< 0.05

Poor neurological outcome is defined by mRS = 3–4–5–6, 12 months after the onset of SAH. GCS: Glasgow coma score on admission. Age was considered as a continuous variable.

Table 4
Multivariate analysis of risk factors associated with lack of one-year self-perceived recovery of previous health status in a single centre cohort of 208 patients with SAH.

	Odds ratio	95% confidence of interval	*P*
Female sex	2.3	1.2–4.3	0.01
GCS ≤ 8	8.3	1.6–20	< 0.01
VAP	6.2	2.7–15.9	< 0.001
Intra-cranial hypertension	3	2.1–17.5	< 0.001
Vasospasm	2.6	1.2–5.5	0.01

VAP: ventilator-acquired pneumonia; GCS: Glasgow coma score on admission.

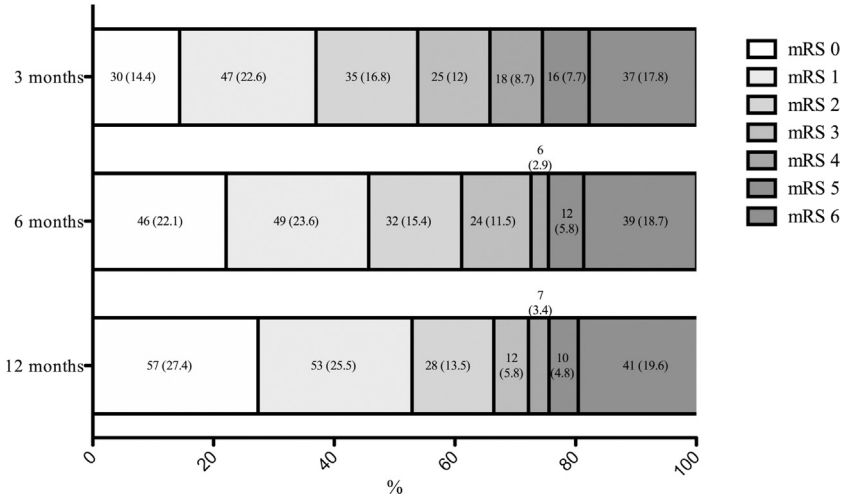

Fig. 1. Evolution of the modified Rankin Scale over the first year following subarachnoid haemorrhage. Number (%) of patients according to each level of the mRS, 3, 6 and 12 months after the onset of SAH.

Table 5
Evolution of patients' cognitive dysfunctions at 3, 6 and 12 months after the onset of SAH.

	3 months	6 months	12 months
Perceived previous health status recovery	33 (19.3)	51 (30.2)	59 (35.3)
Behaviour disturbances	110 (64.3)	105 (62.1)	96 (57.5)
Memory losses	100 (58.5)	82 (48.5)	71 (42.5)
Speech disorders	59 (34.5)	49 (29.0)	41 (24.6)
Sleep disorders	52 (30.4)	39 (23.1)	26 (15.6)
Resume previous job	30 (17.8)	51 (30.3)	62 (37.3)
Return to previous daily activities	71 (41.8)	108 (64.3)	124 (74.7)

mRS: modified Rankin Scale. All items were declarative and collected during a pre-planned questionnaire gathered during phone call. Data are expressed as N (%).

long-term outcome have been poorly described so far. In a monocentric study, Degos et al. [21] found that hydrocephalus was associated with poor outcome in elderly patients. Our result also suggest that hydrocephalus is also a key complication that should be treated promptly. Other risk factors have been delineated such as age [21], intra-cranial hypertension which remains a crucial target in neuro-ICU [22], and poor baseline GCS [23]. Further multicentric observational studies with systematic evaluation at several time-points, could be useful to define the best follow-up in neuro-ICU patients.

We also studied the perceived previous self-perceived health status recovery because this is probably the main concern of patients and relatives at the very early phase of the disease. This question is not well assessed in the literature, because the evaluation of health, as defined by the World Health Organization – "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" – remains highly complex. Although simplistic and questionable, we felt that the only one who could reasonably answer the question, was the patient himself and decided to ask this question in a simplistic manner. Some risk factors were very similar to those retrieved in poor neurological outcome assessed with the mRS. Other specific factors such as female sex, have already been identified in previous studies, without clear explanation [24]. Also, the occurrence of VAP was identified as a potential risk factor of lack of self-perceived previous health status recovery, and was already identified as a factor of poor neurological recovery after SAH [25]. In any case, the information about full health recovery should be cautiously delivered to relatives.

In our work, a little proportion of patients resume their previous work. In spite of geographical differences of health-care and social systems between countries, we found a similar proportion of patients [3]. We have also detailed several symptoms of cognitive dysfunctions during the recovery phase. As it was previously described, patients in our cohort have sustaining troubles (mood disorders, memory losses…). In our cohort, several items like memory losses or speech disorders could not be accurately evaluated during phone interviews. All items were declarative in order to retrieve a maximum of information during these interviews. Interestingly, the proportion of patients suffering from

these cognitive impairments in our cohort, reveals within line of previously published studies [3].

Our study has limitations. Since the evaluation was performed with phone call and items were purely declarative, we cannot ascertain that all questions of the pre-planned questionnaire were adequately understood or told by the patients and relatives. However, the fact that only one physician performed all phone calls, and that the patients were interviewed several times could have limited interpretation bias. Also, the risk factors identified in the multivariate analysis suggest association and not causation, and some previously published studies targeting specific SAH complications have failed to demonstrate neurological improvement [26]. The diagnosis of DCI was not standardised during the study period and many patients did not undergo MRI. This could lead to discrepancies in the diagnosis and explain why DCI was not retrieved as a risk factor of poor outcome. Also, the diagnosis of vasospasm remains challenging [27] and was left to the discretion of the radiologist during the study period. This could explain the discrepancies in the relationship between vasospasm and poor outcome [28] and why vasospasm-targeted therapies have failed to improve outcome [26]. Although vasospasm yields conflicting results, this complication should be screened and treated. Eventually, this is a monocentric cohort, without an external validation cohort: others may not retrieve these results.

5. Conclusion

Our study highlights several risk factors already pointed in the literature as factors or poor prognosis. We once again point out the high prevalence of cognitive disorders, mood disorders and memory losses after SAH. Further studies focusing on cognitive disorders after SAH should be performed to better understand the factors associated with neurological outcome.

Ethical statement

The autors acknowledge that this study was approved by the local ethics committee of the University Hospital of Nantes. Since the study was purely observational, consent was not mandatory, but all patients or next-of-kin received information about the study and follow-up.

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Author's contribution

RC designed the study, included patients, performed follow-up, analysed the data and wrote de the article. JBP included patients performed follow-up, analysed the data and wrote the article. KL included patients and edited the article. HD, AC edited the article. RC, DF, BA performed statistical analysis. BR, KA analysed data and wrote the article.

Disclosure of interest

Karim Asehnoune has received grants from LFB, Fresenius and Baxter. Bertrand Rozec has received grants from LFB, Fresenius, Baxter, Xenios, Fisher & Paykel. The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, https://doi.org/10.1016/j.accpm.2018.10.002.

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