Master di I livello

Neurofisiologia clinica in area critica e terapia intensiva

Early brain injury after subarachnoid hemorrhage: a single centre observational study

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ABSTRACT

Introduction

Subarachnoid hemorrhage still has high poor prognosis rates. Early brain injury has recently come to attention, but data on prevalence, risk factors and long-term outcomes are still lacking, particularly to what concerns seizures and vasospasm.

Methods

Single centre retrospective study including consecutive patients with moderate to poor grade SAH defined according to WFNS, Hunt and Hess and modified Fischer scale. EBI was defined as any ischemic lesion appearing within 72 hours from SAH repair. Daily EEG, CT and TCD data were extracted. Long-term good functional outcome was defined as GOSE score 5 or higher.

Results

We included 37 individuals with moderate to severe SAH (mean age=56 years, women 62.2%). Hunt-Hess mean grade was 3.6, GCS mean grade was 9.9. Four patients died after SAH (10.2%), while favorable outcome was reached by 18 patients (48.6%). EBI was found in more than half of patients (n=19, 51.4%), and 6 developed overt seizures. No single factor significantly predicted EBI related to SAH in logistic regression. However, when also epileptic activity is considered, its impact on the development of ischemia seems significant (LogRank p=0.01).

Conclusions

Predictors for EBI are needed to find windows to reduce mortality and disability from SAH. Tailored seizure prophylaxis may represent a factor worth of further investigations.

BACKGROUND

Subarachnoid hemorrhage essentials

Subarachnoid hemorrhage (SAH) is a medical emergency characterized by bleeding into the space between the brain and the thin tissue covering the brain (subarachnoid space). SAH can result from a ruptured aneurysm, trauma, or other underlying conditions. It is a serious condition that requires immediate medical attention and can cause disability or even death.

SAH is a relatively rare condition, accounting for only 5% of all strokes. The estimated annual incidence of SAH is 6 to 16 cases per 100,000 people worldwide. The incidence is higher in women than in men, and the peak age of onset is between 40 and 60 years[1]. SAH is more common in people with a family history of the condition or a history of smoking, hypertension, or heavy alcohol use.

The incidence of SAH is rare, but it carries a high morbidity and mortality rate. SAH can be caused by various factors, including aneurysms, head trauma, and other underlying conditions.

Aneurysms are the most common cause of SAH. Aneurysms refer to the ballooning out of a weakened area in a blood vessel, which can eventually burst and cause SAH. Aneurysms can be congenital or acquired, and they are often asymptomatic until they rupture, but genetic factors driving their development can also drive the risk of rupture[2]. Age is also an important risk factor for SAH, as the incidence of the condition increases with age. Furthermore, sex is another factor that affects the risk of SAH, with women being more likely to develop SAH than men. Additionally, having a family history of SAH is also linked to an increased risk of developing the condition. Environmental factors such as smoking, hypertension, heavy alcohol use, and cocaine use have been identified as

significant risk factors for SAH. Smoking increases the risk of SAH by two to three times in comparison to non-smokers[3]. High blood pressure is also a known risk factor for SAH, as it can increase the risk of rupturing an aneurysm. Heavy alcohol use can increase the risk of SAH by damaging blood vessels and causing hypertension. Cocaine use can cause sudden increases in blood pressure, leading to an increased risk of SAH.

SAH represents a catastrophic event, associated with high mortality and poor rates of full recovery[4]. Most of SAH cases are related to the rupture of an aneurysm in the main branches of intracerebral arteries, a condition which might be suitable to emergent intervention via clipping or coiling procedures[5]. Case fatality had a yearly 0.9% decline over the past two decades, mainly in relation to timely diagnosis and significant improvement in devices[1,4]. Despite optimal management, however, the rates of good functional recovery remain unsatisfactory. Studies from high-income countries report rates of death as high as 25%, with almost two thirds of patients left with neurological deficit with some impact on daily activities. Such outcomes weight heavy on SAH patients, which are on average 20 years younger than people suffering from ischemic stroke, therefore translating into a longer burden of chronicity, disability, and cost to society[4].

Delayed cerebral ischemia and early brain injury after SAH

After the development of coiling, which grossly reduced mortality after aneurysmal SAH, a further attempt to mitigate the risk of poor neurological outcome after SAH came from the management of vasospasm. Vasospasm can develop in two thirds of people with aneurysmal SAH, mainly in relation to a local driver, blood. Indeed, haemoglobin, its degradation products, and erythrocytes, can elicit local endothelial reaction, leading to narrowing of arteries next to the site of the aneurysm. As vasoconstriction progresses,

blood supply to distal cortex may become insufficient, leading to local ischemia. This pathophysiological mechanisms, based on direct correspondence between vasospasm, delayed cerebral ischemia (DCI) and poor functional outcome, led to landmark studies, which proposed nimodipine as a potential tool to limit angiographic vasospasm and improve overall prognosis[6]. Over the following decades nimodipine was confirmed as the only drug able to improve neurological outcome, but failed to be consistently associated with a control of vasospasm[7], putting the consequentialist logic of vasospasm-DCI under debate. Agents aimed at controlling endothelial factors also failed to mitigate vasospasm or mortality [8], and vasospasm control failed to translate into consistent reduction of mortality[7], further supporting research into complementary mechanisms. Indeed, two thirds of SAH patients develop vasospasm, but only than one third develops DCI, implying that other mechanisms should take part in the process[9–12].

As DCI and vasospasm can happen on a relatively wide temporal window, 3 to 14 days after SAH, research has focused on early events that may pave the way to complications with negative impact on outcome. The acute effects of subarachnoid blood and the transient ischemia that may accompany aneurysm rupture (referred to as early brain injury, EBI) can develop already in the first 72 hours[13]. Despite its definition is elusive, with neuroimaging, clinical and biomarker criteria applied with poor consistency even across studies, EBI seems to represent a key determinant for poor prognosis on the long-term[13]. Therefore, what happens in the very early phase seems to produce events and have an impact way beyond the first days after SAH.

EBI refers to the pathological changes that occur within the first 72 hours after SAH, before the onset of DCI. These pathological changes include cerebral edema, microvascular dysfunction, oxidative stress, and inflammation, which can lead to neurovascular

uncoupling, cerebral hypoperfusion, and neuronal death. These events occur through the activation of various cellular signaling pathways, and are thought to be a result of blood-brain barrier disruption, erythrocyte lysis, and iron toxicity following hemorrhage[13]. EBI has been associated with higher incidence of DCI and poor neurological outcomes, suggesting that addressing risk factors early during SAH course would result in potential synergic effects on prevention of both EBI and DCI[4].

Despite EBI constructs dates back to a decade ago, there is still substantial heterogeneity on its definition[13,14]. To this extent, EBI clearly differentiates from DCI. Risk factors for DCI are well defined, and included volume, density and persistence of the subarachnoid thrombus, pre-existing hypertension, and EBI itself[4]. However, what are the upstream factors driving EBI occurrence is still uncertain.

Seizure and ischemia can be regarded as very early features in the course of SAH. Seizures can develop even in advance of treatment, or represent the onset symptom[15]. The risk of seizures tends to increase soon after treatment, a condition which therefore highlights the potential involvement in driving EBI. At the same time, not all cases of ischemia developing after SAH are driven by vasospasm. Indeed, early ischemia can represent the results of acute changes in intracranial pressure, hyperacute arterial narrowing and loss of blood supply happening immediately after SAH. Therefore, early ischemia may as well represent a potential contributor to EBI.

Aims of the study

The aim of this pilot study is to define the prevalence of EBI, seizures and vasospasm in a cohort of consecutive patients undergoing aneurysmal repair after SAH. The major aim is to weight the impact of these factors on the development of EBI and DCI, to drive further investigations and potential interventions.

METHODS

Cohort selection and data extraction

Patients consecutively admitted to the Bufalini Hospital, Cesena, AUSL Romagna, were retrospectively selected and included in this study. The Bufalini Hospital is a non-academic hospital acting as the Hub of an health network serving 1.2 million inhabitants in the provinces of Ravenna (north), Forlì-Cesena (mid) and Rimini (south) of the Romagna region. Bufalini Hub services include trauma, stroke, neurointerventional emergencies and neurosurgical emergencies; emergency cardiology is deflected towards two other hospitals in the AUSL Romagna health network, while cardiosurgical emergencies are managed by GVM private hospital as no cardiosurgery unit lies within the AUSL No specific local procedure is available for the management of SAH patients, which is left to neurologists, neurosurgeons and intensive care professionals according to clinical status and prognostication prospects.

For the purpose of this pilot study, I retrospectively reviewed charts of all SAH patients admitted in the timeframe 2019-2020. All patients with SAH with no interventional diagnostic of therapeutic procedure, either endovascular or neurosurgery, were excluded. I selected medium to severe cases, defined by the occurrence of both GCS below 13 at presentation and modified Fischer scale of 2 or higher, undergoing neurosurgical or endovascular procedures for rebleeding prevention.

Demographic, clinical and neuroradiological details were collected from medical records. Electroencephalography (EEG), transcranial doppler studies (TCD) and neurovascular imaging, including digital subtraction angiography, non-contrast and contrast computer tomography of the brain, and brain magnetic resonance imaging were all re-evaluated

blinded to patients outcome by a single operator with experience in neurocritical care, with three random-order revision rounds to ensure intra-rater consistency in adjudication.

Index SAH was rated according to World Federation of Neurological Surgeons (WFNS) grading scale for SAH, an ordinal discrete scale based on Glasgow Coma Scale (GCS) and motor deficit which is the most widely applied SAH prognostic scale[16].

All cases were followed up with the extended Glasgow outcome (GOSE) scale [8]. Quality of life was assessed with Euroqol measure, with all outcomes (GOSE, EQOL and EQOL with visual assessment scale, EQOL-VAS) reported at 12 months after SAH[15]. SAH severity was also adjudicated according to Hunt and Hess Scale, a grading scale considering neurological deficit on examination ranging from consciousness to focal neurological deficit. Moreover, SAH severity was also rated according to the modified Fisher scale, a neuroradiological scale expected to predict complications and vasospasm, with higher scores for thick SAH and intraventricular hemorrhage[15].

Aneurysmal site was considered for the bleeding only aneurysm, and was adjudicated according to digital subtraction angiography (DSA), non-contrast computerized tomography (NCCT) and computerized tomography angiography (CTA) reports. In cases of multiple aneurysmal sites, SAH was adjudicated to pertain to univocal site, with advanced imaging modalities (fusion imaging, black-blood brain magnetic resonance imaging) implemented to guide bleeding site definition. Intracranial pressure was monitored invasively or non-invasively on a case-by-case, depending on neurosurgical approach and availability of non-invasive monitoring devices. ICU stay and hospital stay were measured in days and collected to derive surrogate measures for costs.

Definition of independent variables and outcomes

Clinical deterioration was defined as a new focal neurological deficit, or GCS decrease of at least two points, or national institute of health score (NIHSS) decrease of at least 2 points, independently from symptom localization.

Ischemia was defined as a new ischemic lesion reported on plaint CT or brain MRI compared to the original or previous brain imaging available. Early brain ischemia was adjudicated whenever ischemic lesions developed within the first 72 hours, with features in agreement with evolution of a new ischemic lesion after intervention. If clinical changes developed, ischemic lesion was defined as symptomatic whenever lesion territory was compatible with new signs/symptoms, independently from reaching the abovementioned criteria for clinical deterioration.

NCCT was commonly used to monitor day-by-day the evolution of SAH in the first 5-7 days, with timing of diagnostics left to the treating physicians and manager of interventions.

Vasospasm was defined according to transcranial doppler sonography (TCD), CTA, DSA or CT perfusion findings, with TCD mainly used for daily monitoring [17]. Vasospasm onset was defined as the first day with intracranial velocities reaching criteria for vasospasm, with mild, moderate and severe grading according to peak systolic, mean flow velocities and Lindegaard ratio. Vasospasm resolution was adjudicated according to DSA or non-invasive monitoring, according to original reports.

Dates of electroencephalography assessment were registered, with local protocols including early (<24h) EEG recording for all patients with SAH, independently from SAH severity. Prophylaxis with antiseizure medicaitons (ASM) or any ASM use before EEG recording was also registered to adjust for analysis. Overt seizures were considered all cases of seizures during ICU monitoring with clinically overt semiology, excluding cases of

non-convulsive status epilepticus. EEG recordings were rated according to the 2021 American Society of Neurophysiology Standardized terminology [18], based on the original report and whole-length EEG recording. The first three recording of each participant were rated separately from a single rater, with reiteration of rating in three separated random-based sequence sessions to ensure intra-rater consistency. A binary variable termed “epileptic activity” was adjudicated in cases with overt seizures, NCSE or epileptiform discharges (EDs) defined according to standardized terminology in all EEG available within the first 72 hours.

Early brain injury (EBI) was defined as a clear and manifest brain ischemia developing after intervention and not strictly associated with the operative procedures, with evolution in following scans consistent with persistent edema, brain ischemia or new hemorrhage. Time to ischemia was defined according to the first available scan with changes consistent with the definition in the first 72 hours. I collected all scans following the first 30 days after SAH and data were extracted also regarding later ischemia, either vasospasm-related or non-related to vasospasm.

The primary outcome was acceptable functional recovery, defined as a mild to moderate disability according to GOSE score of 5 or higher. Secondary outcomes were: development of any ischemia, early brain injury, overt seizures and epileptic activity, and vasospasm. We also included time metrics and additional outcomes, including length of stay in ICU and hospital, volume of ischemia according to standardized volumetric calculation, and 12-mont quality of life according to EQOL questionnaires.

Statistical analysis

Sample size calculation was not available as studies on early brain injury are lacking definition and present substantial confounders that limit the generalizability of sample size estimation. This is particularly relevant in the case of a pilot study in a single institution, with no internal or external funding.

Data are presented as count and percentages for ordinal and categorical variables, and as means and standard deviations for continous and semi-continous variables. Student T-test and original χ^2 tests were used to compare mean and standard deviaitions and ordinal or categorical variable distribution in the cohort. Univariate analysis was set-up to investigate risk factors for the development of EBI and primary outcome. Regression analysis was a priori defined to include all factors emerging from univariate analysis as predictors of the primary outcome, to build a model to test for prediction of the outcome of interest. Kaplan Meier survival curves were used to distinguish trajectories of time to ischemia in patients presenting the factors of interest: EBI, overt seizures, and vasospasm. Log-Rank testing was defined a priori to be implemented in survival analysis according to censoring to the first 30 days, which reasonably attributes the same value to all events across the observation period.

Statistical analysis was performed with R version 3.3.1 and SPSS version 26.

Funding and ethical clearance

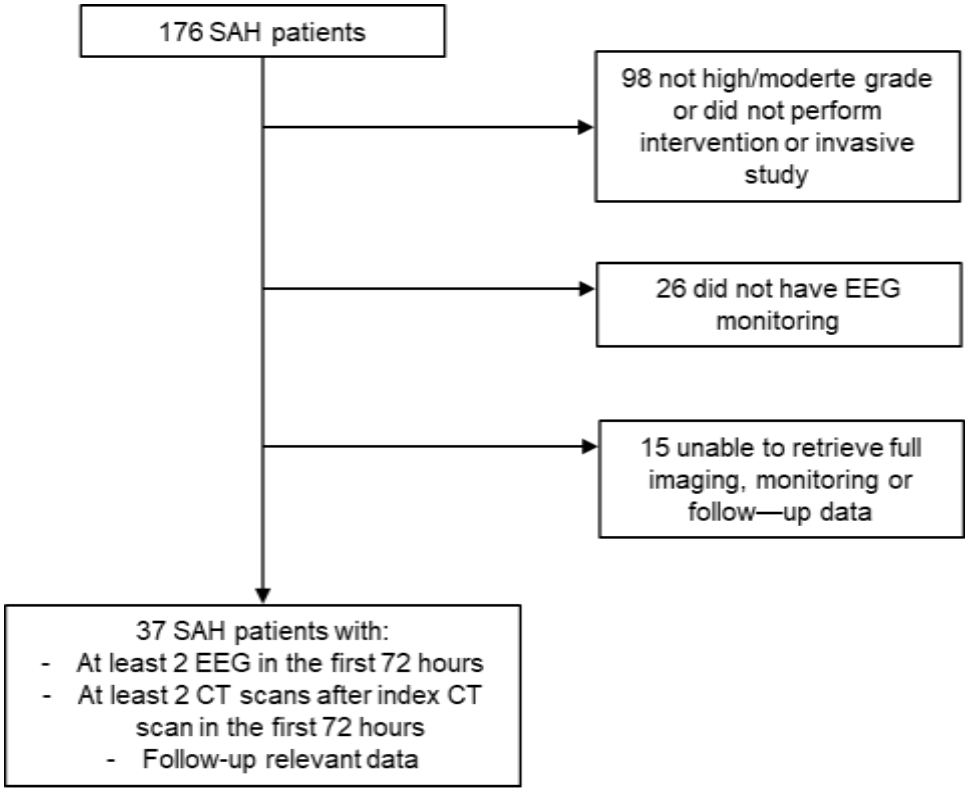
This study only uses anonymized data, and as for the retrospective nature, only needed notification to the internal board, which was pursued accordingly. This study was not eligible for internal funding as per informal request with AUSL Romagna, and was

developed outside of clinical working hours. MR has no conflict of interest to report relevant to this research, and has received no funding for this project.

RESULTS

In the considered timeframe between 2019 and 2020, 176 patients with SAH were admitted to our single center. Among them, 37 (21.0%) were found to meet criteria for eligibility in this pilot study, and were their records were therefore fully retrieved (Figure 1 for flowchart summarizing patient selection). Selection was based on moderate to severe SAH with availability of ICU monitoring, early EEG recordings and neuroimaging, and full outcome data.

Figure 1. Flowchart for cohort selection



Cohort characteristics

Our cohort consisted in 37 individuals with moderate to severe SAH, mean age 56 years and mainly women (62.2%) (Table 1 for summary of characteristics of the study cohort)

People in our cohort presented frequent cardiovascular risk factors, including hypertension (54%) and smoking (29.7%). WFNS mean grading was 3, while Hunt and Hess mean grade was 3.6. The corresponding admission GCS was fairly low (mean 9.9), highlighting the fact that our cohort is mostly represented by poor grade SAH. Eighteen patients underwent endovascular procedure with coiling (48.6%), while all the remaining underwent neurosurgery. SAH localization was mostly supratentorial and pancisternal, with only two cases with bleeding limited to infratentorial localization. Accompanying intraparenchymal hemorrhage was present in 43.2% of cases (Table 1)

Table 1. Characteristics of the cohort

Cohort (n=37)	
Age	56.1 ± 14
Gender (female)	23 (62.2%)
Smoking	11 (29.7%)
Hypertension	20 (54.1%)
Diabetes	2 (5.4%)
WFNS	3 ± 1.6
Hunt-Hess	3.6 ± 1.3
GCS	9.9 ± 4.5
modified Fischer scale	3.6 ± 0.8
Interventional approach	1 (2.7%)
EVT	18 (48.6%)
Time to intervention	0 ± 0
Hydrocephalus	23 (62.2%)
External ventriculr drainage	23 (62.2%)
Intracranial hypertension (0-24h)	12 (32.4%)
Intracranial hypertension (>24h)	9 (24.3%)
Non-infective fever	26 (70.3%)
Hyponatriemia	17 (45.9%)
Therapeutic hypertension	11 (29.7%)
ICH	16 (43.2%)
SAH site	
infratentorial	2 (5.4%)
left-sided	8 (21.6%)
pancisternal	19 (51.4%)
right-sided	8 (21.6%)

Cohort outcomes

Endovascular rescue therapy was performed in only 2 patients, while all remaining needed no reintervention. All interventions were performed within 24 hours from SAH onset, independently from the approach preferred.

In our cohort, four patients died after SAH (10.2%). Favorable outcome, defined as GOS higher than 4, was reached by 18 patients (486%), with 35% of them also reaching an optimal recovery, as defined by GOSE score 7 to 8.

EBI was found in more than half of patients (n=19, 51.4%), with clinical deterioration in six of them. Brain ischemic lesion could also develop over longer period, as suggested by a slightly increased rates of ischemia over 30 days (any ischemia n=25, 67.6%). Vasospasm developed in 15 patients, and recurred in two.

Up to 76% of patients received antiseizure medications (ASM) as prophylaxis. Five overall developed overt seizures, with 78.4% showing some electroencephalographic or clinical signs of epilepsy. Five patients developed NCSE, which was in all cases treated and resolved with benzodiazepine and sedation.

Table 2. Outcomes of the cohort

Outcome data	
GOSE 12 months	4.6 ± 2.7
Good recovery (GOSE 7-8)	13 (35.1%)
Favorable outcome (GOSE>4)	18 (48.6%)
EQOL-Index	0.6 ± 0.5
EQOL-VAS	74.6 ± 21
Early brain ischemia (<72h)	19 (51.4%)
Clinical deterioration	6 (16.2%)
Any ischemia	25 (67.6%)
Time to ischemia	12.1 ± 12.8
Symptomatic ischemic lesion	17 (68%)
Asymptomatic ischemic lesion	8 (32%)
Ischemia volume (largest, ml)	44.5 ± 59.7
Vasospasm	
mild	4 (10.8%)
moderate	4 (10.8%)
severe	7 (18.9%)
Recurrent vasospasm	2 (11.8%)
Prophylaxis or ASM before EEG	28 (75.7%)
Overt seizures	5 (13.5%)
Epileptic activity (either overt seizures, NCSE or Electrical activity)	29 (78.4%)
NCSE	5 (13.5%)
definite	2 (5.4%)
possible	3 (8.1%)
Endovascular rescue therapy	2 (5.4%)
ICU stay (days)	14.4 ± 7.2
Hospital stay (days)	29.7 ± 25.9

Risk factors for Early Brain Injury

In this cohort, people with EBI had similar cardiovascular risk factors compared to those not developing this complication. However, people with EBI were less frequently treated with endovascular coiling, had higher rates of early intracranial hypertension, and more frequently received prophylactic ASM, a condition which may suggest reverse causality (Table 3). Both vasospasm and any epileptic activity were both marginally more frequent in people developing EBI, which was also more common among those with higher Hunt and Hess score at admission (Figure 2).

Figure 2. EBI distribution according to Hunt-Hess scale

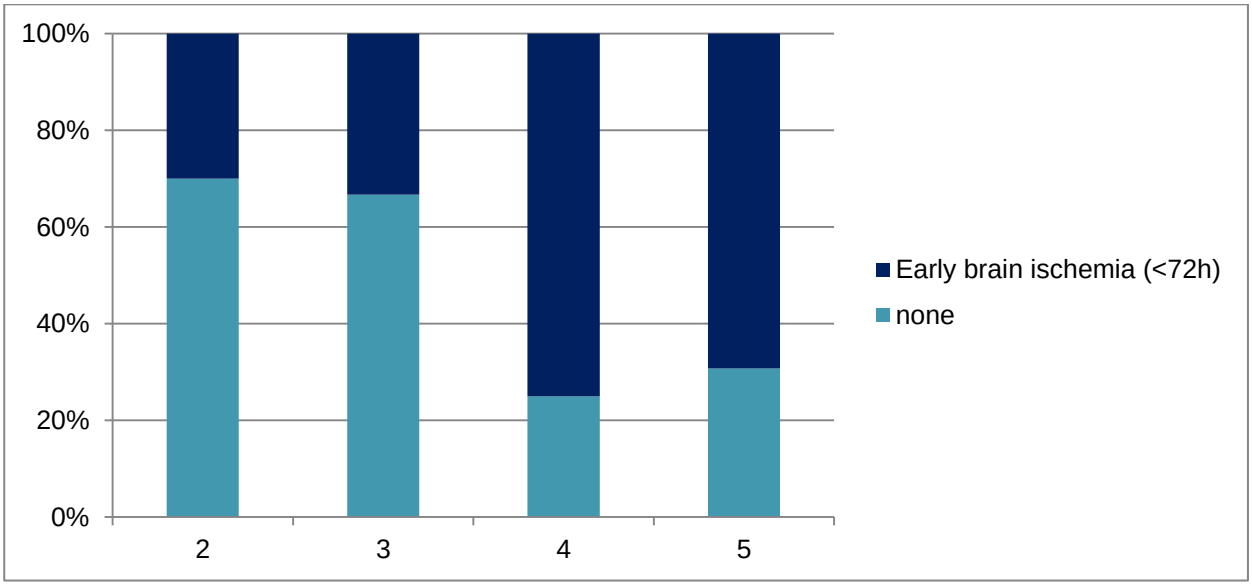


Table 3. Characteristics of people developing EBI

	no EBI (n=18)	**EBI (n=19)**	p-value
Age	60 ± 12.3	53 ± 14.9	ns
Gender	12 (66.7%)	11 (57.9%)	ns
Smoking	6 (33.3%)	5 (26.3%)	ns
Hypertension	11 (61.1%)	9 (47.4%)	ns
Diabetes	2 (11.1%)	0 (0%)	ns
WFNS	2.4 ± 1.6	3.6 ± 1.4	ns
Hunt-Hess	3.1 ± 1.2	4 ± 1.2	ns
GCS	11.3 ± 4.2	8.5 ± 4.4	ns
modified Fischer scale	3.3 ± 0.9	3.9 ± 0.5	ns
Endovascular approach	12 (66.7%)	6 (31.6%)	0.038
Time to intervention	0 ± 0	0 ± 0	ns
Hydrocephalus	11 (61.1%)	12 (63.2%)	ns
External ventriculr drainage	11 (61.1%)	12 (63.2%)	ns
Intracranial hypertension (0-24h)	2 (11.1%)	10 (52.6%)	0.016
Intracranial hypertension >24h)	3 (16.7%)	6 (31.6%)	ns
Non-infective fever	10 (55.6%)	16 (84.2%)	ns
Hyponatriemia	7 (38.9%)	10 (52.6%)	ns
Therapeutic hypertension	3 (16.7%)	8 (42.1%)	ns
ICH	5 (27.8%)	11 (57.9%)	ns
SAH site			ns
infratenetorial	2 (11.1%)	0 (0%)	ns
left	3 (16.7%)	5 (26.3%)	ns
pancisternal	9 (50%)	10 (52.6%)	ns
right	4 (22.2%)	4 (21.1%)	ns
Endovascular rescue therapy	2 (11.1%)	0 (0%)	ns
Outcomes	**no EBI (n=18)**	**EBI (n=19)**	
GOSE 12 months	5 ± 2.6	4 ± 2.7	ns
Good recovery (GOSE 7-8)	9 (50%)	4 (21.1%)	ns
Favorable outcome (GOSE>4)	12 (66.7%)	6 (31.6%)	ns
EQOL-Index	0.6 ± 0.5	0.5 ± 0.5	ns
EQOL-VAS	75 ± 25.4	74 ± 14	ns
ICU stay (days)	13 ± 8.8	16 ± 4.8	ns
Hospital stay (days)	25 ± 18.1	34 ± 31.5	ns
Clinical deterioration (New focal neurological deficit OR GCS 2 points OR NIHSS 2 points)	2 (11.1%)	4 (21.1%)	ns
Any ischemia	6 (33.3%)	19 (100%)	ns
Symptomatic ischemic lesion	2 (33.3%)	15 (78.9%)	ns
Vasospasm	5 (27.8%)	10 (52.6%)	ns
Vasospasm grading			ns
mild	3 (16.7%)	1 (5.3%)	ns
moderate	1 (5.6%)	3 (15.8%)	ns
severe	1 (5.6%)	6 (31.6%)	ns
Recurrent vasospasm	2 (40%)	0 (0%)	ns
Prophylaxis or ASM before EEG	10 (55.6%)	18 (94.7%)	0.005
Overt seizures	3 (16.7%)	2 (10.5%)	ns
Epileptic activity (either overt seizures, NCSE or Electrical activity)	12 (66.7%)	17 (89.5%)	ns
NCSE			ns
definite	2 (11.1%)	0 (0%)	ns
possible	2 (11.1%)	1 (5.3%)	ns

Factors associated with good functional recovery

Good functional recovery, as defined by GOSE scores higher than 4 at 12 months (n=18), was more frequent in people with lower Hunt and Hesse scale scores (p=0.022), with early intracranial hypertension and EBI (Table 4). However, when included in logistic regression analysis, no single factor reached a statistically significant position in predicting EBI related to SAH (Table 5).

Table 4. Distribution of clinical and radiological factors for outcome

	GOSE 1-4 (n=19)	**GOSE 5-8 (n=18)**	**p-value**
Age	55 ± 16.9	57 ± 10.5	ns
Gender	10 (52.6%)	13 (72.2%)	ns
Smoking	7 (36.8%)	4 (22.2%)	ns
Hypertension	9 (47.4%)	11 (61.1%)	ns
Diabetes	0 (0%)	2 (11.1%)	ns
WFNS	3.4 ± 1.6	2.6 ± 1.5	ns
Hunt-Hess	4 ± 1.2	3.1 ± 1.1	0.022
GCS	8.8 ± 4.9	11.1 ± 3.8	ns
modified Fischer scale	3.8 ± 0.6	3.4 ± 0.9	ns
Intracranial hypertension (0-24h)	10 (52.6%)	2 (11.1%)	0.007
Hyponatriemia	10 (52.6%)	7 (38.9%)	ns
Therapeutic hypertension	6 (31.6%)	5 (27.8%)	ns
ICH	11 (57.9%)	5 (27.8%)	0.05
Endovascular rescue therapy	0 (0%)	2 (11.1%)	ns
Outcomes	**GOSE 1-4 (n=19)**	**GOSE 5-8 (n=18)**	**p-value**
EQOL-Index	0.1 ± 0.5	0.8 ± 0.3	<0.001
EQOL-VAS	54 ± 23.3	84 ± 11.5	<0.001
ICU stay (days)	17 ± 5.1	12 ± 8.2	0.032
Hospital stay (days)	34 ± 33.7	26 ± 13.6	ns
Early brain ischemia (<72h)	13 (68.4%)	6 (33.3%)	0.033
Any ischemia	15 (78.9%)	10 (55.6%)	ns
Symptomatic ischemic lesion	12 (80%)	5 (50%)	ns
Vasospasm grading			ns
mild	2 (10.5%)	2 (11.1%)	ns
moderate	2 (10.5%)	2 (11.1%)	ns
severe	5 (26.3%)	2 (11.1%)	ns
Recurrent vasospasm	0 (0%)	2 (28.6%)	0.072
Clinical deterioration (New focal neurological deficit OR GCS 2 points OR NIHSS 2 points)	3 (15.8%)	3 (16.7%)	ns
Prophylaxis or ASM before EEG	14 (73.7%)	14 (77.8%)	ns
Overt seizures	3 (15.8%)	2 (11.1%)	ns
Epileptic activity (either overt seizures, NCSE or Electrical activity)	15 (78.9%)	14 (77.8%)	ns
NCSE			
definite	1 (5.3%)	1 (5.6%)	ns
possible	2 (10.5%)	1 (5.6%)	ns

Table 5. Logistic regression for good functional outcome

Factor	OR (95%CI)
Age	0.98 (0.91-1.06)
Overt seizures	0.4 (0.04-3.85)
Hunt-Hess	0.55 (0.27-1.09)
ICH	0.32 (0.06-1.78)
Early brain ischemia (<72h)	0.28 (0.05-1.51)
Vasospasm	1.04 (0.14-7.67)

Factors associated with development of ischemia

Overt seizures seem to carry an only marginal increase in the risk of developing ischemic lesions after SAH (LogRank p=0.12). However, the group receiving prophylaxis had higher rates of ischemic lesions compared to those not receiving prophylaxis (LogRank p=0.013; Figure 3). At the same time, when all potential epileptic activity is considered, its impact on the development of ischemia seems significant (LogRank p=0.01; Figure 4).

Figure 3. Trajectories of time to ischemia among people with overt seizure and among those receiving prophylactic use of ASM

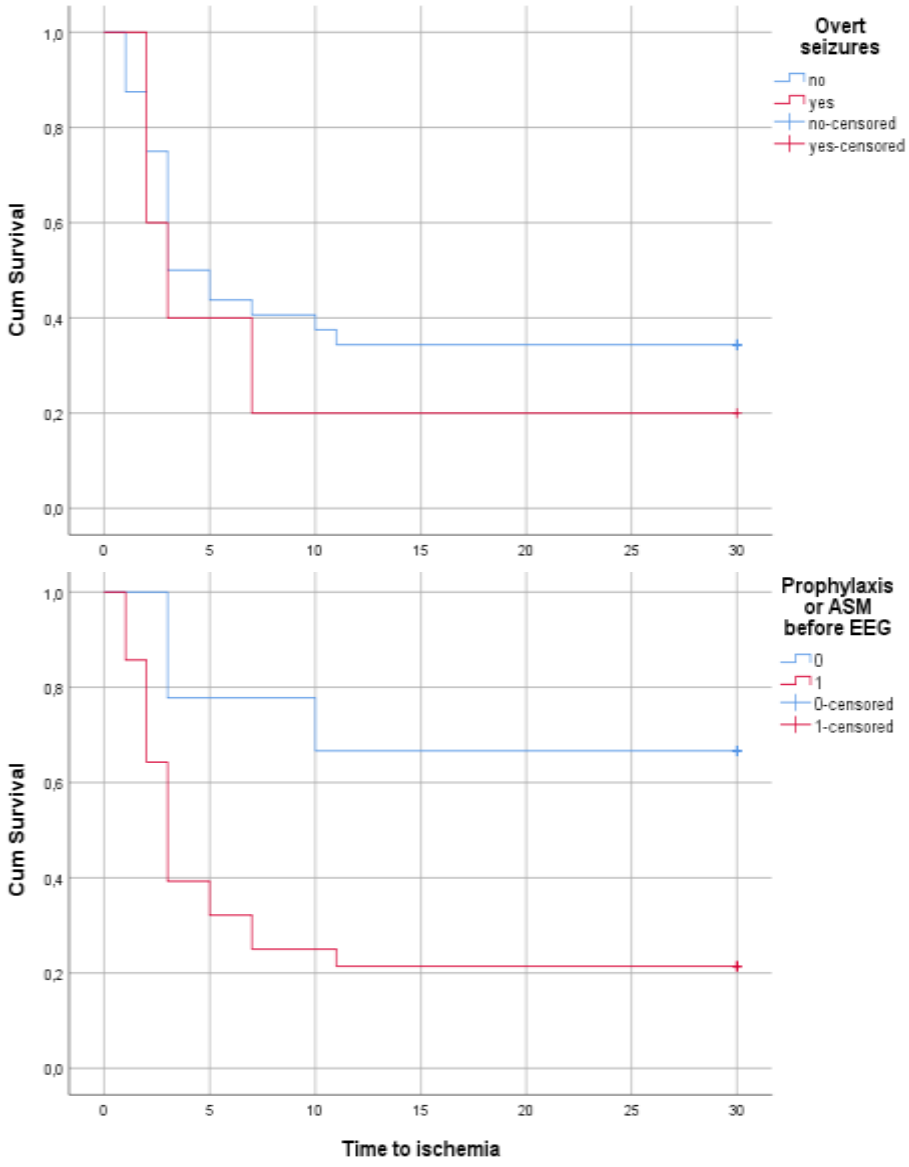
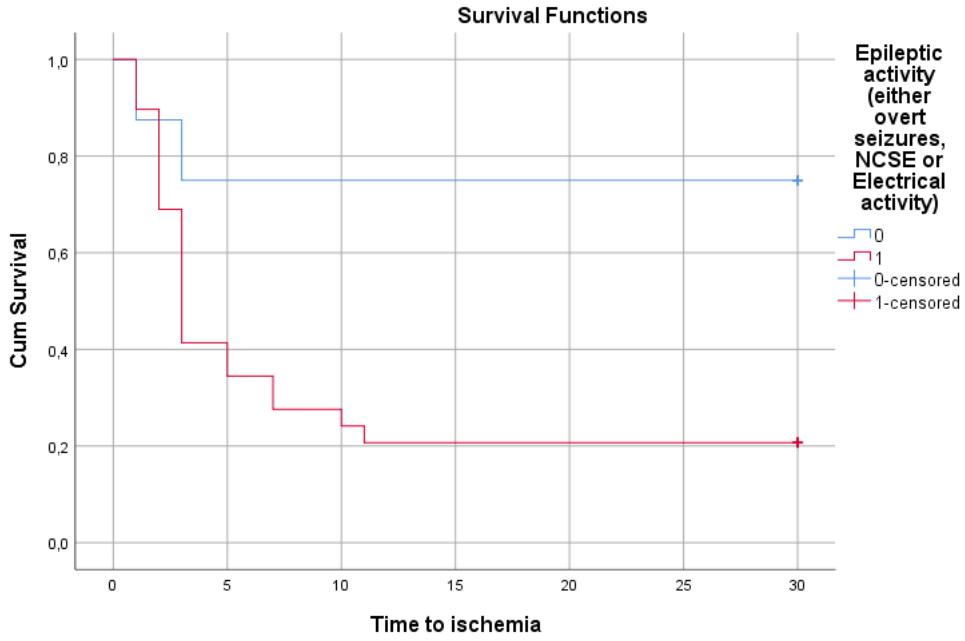
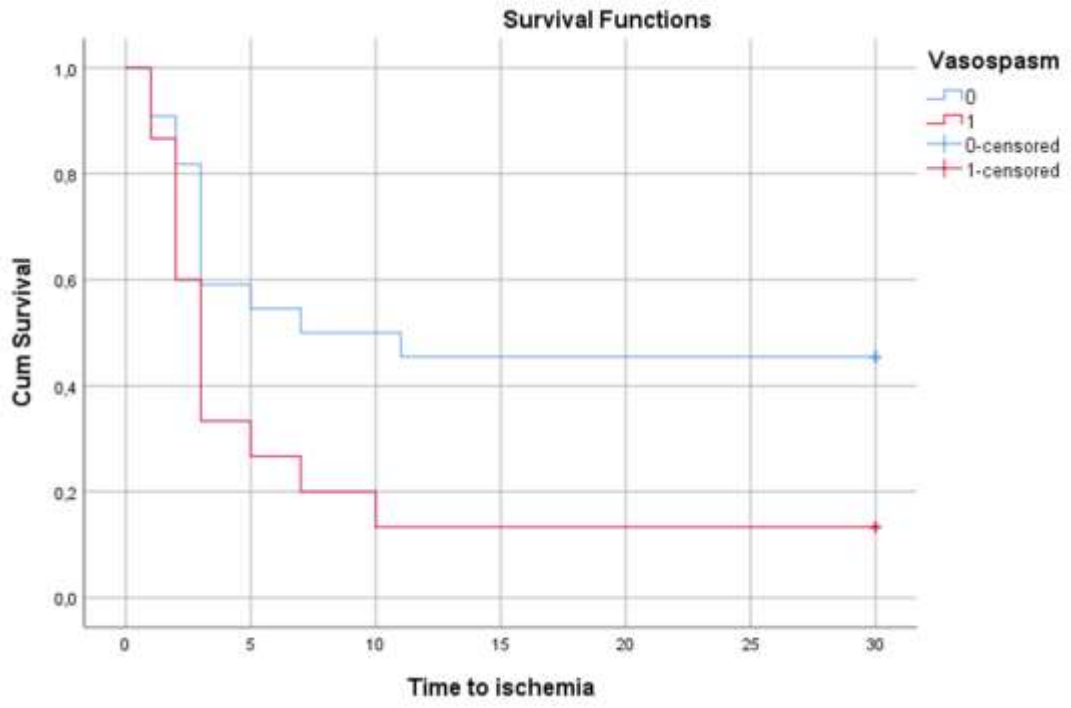


Figure 4. Time to ischemia depending on any epileptic activity.



People developing vasospasm seemed to have a consistently higher chance of developing ischemia compared to those who did not develop vasospasm (LogRank p=0.031; Figure 5).

Figure 5. Time to ischemia depending on the development of vasospasm



CONCLUSIONS

This study highlights that the development of EBI can have an influence on the long term recovery from SAH. The attention of research on SAH has been for decades on prevention of vasospasm, a road that has, however, led to only one drug – nimodipine – able to improve outcome without even directly impacting on vasospasm itself[7]. As SAH still carries unacceptable rates of poor prognosis, efforts are needed to highlight new potential mechanisms and time windows for interventions.

In this study, EBI reduces the chances of good functional recovery by 70% on overall estimates, a size effect that is worth of further investigations for factors contributing to it.

To this extent, it is intracranial hypertension and neurosurgical approach seems those to carry the highest risk of EBI. However, also prophylactic use of ASMs seems to associate with EBI, a finding that clearly seems to reflect reverse causality, with prophylaxis started among those with poorer SAH grades, also at higher risk of EBI. This factor seems indeed to be the most promising. As emerges from survival analysis, the onset of any ischemia seems favoured in the acute and subacute term (30 days from SAH) by epileptic activity. This highlights the potential impact of tailored prevention, as demanding blood supply from neurons invested by epileptiform discharge may critically foster a mismatch in a debilitated intracranial circulation.

Our results also suggest that, although ischemia can happen as early as 48 hours, long before the development of vasospasm, these two factors are indeed intertwined. A peculiar susceptibility to ischemia could be hypothesized to participate in both EBI and DCI, suggesting further efforts in uncovering shared mechanisms[4].

REFERENCES

1. Lovelock, C.E.; Rinkel, G.J.E.; Rothwell, P.M. Time Trends in Outcome of Subarachnoid Hemorrhage: Population-Based Study and Systematic Review. *Neurology* **2010**, *74*, 1494–1501, doi:10.1212/WNL.0b013e3181dd42b3.

2. Medina-Suárez, J.; Rodríguez-Esparragón, F.; Sosa-Pérez, C.; Cazorla-Rivero, S.; Torres-Mata, L.B.; Jiménez-O'Shanahan, A.; Clavo, B.; Morera-Molina, J. A Review of Genetic Polymorphisms and Susceptibilities to Complications after Aneurysmal Subarachnoid Hemorrhage. *Int. J. Mol. Sci.* **2022**, *23*, doi:10.3390/ijms232315427.

3. Vlak, M.H.M.; Rinkel, G.J.E.; Greebe, P.; Algra, A. Risk of Rupture of an Intracranial Aneurysm Based on Patient Characteristics: A Case-Control Study. *Stroke* **2013**, *44*, 1256–1259, doi:10.1161/STROKEAHA.111.000679.

4. Macdonald, R.L. Delayed Neurological Deterioration after Subarachnoid Haemorrhage. *Nat. Rev. Neurol.* **2014**, *10*, 44–58, doi:10.1038/nrneurol.2013.246.

5. Connolly, E.S.; Rabinstein, A.A.; Carhuapoma, J.R.; Derdeyn, C.P.; Dion, J.; Higashida, R.T.; Hoh, B.L.; Kirkness, C.J.; Naidech, A.M.; Ogilvy, C.S.; et al. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* **2012**, *43*, 1711–1737, doi:10.1161/STR.0b013e3182587839.

6. Pickard, J.D.; Murray, G.D.; Illingworth, R.; Shaw, M.D.M.; Teasdale, G.M.; Foy, P.M.; Humphreys, P.R.D.; Lang, D.A.; Nelson, R.; Richards, P.; et al. Effect of Oral Nimodipine on Cerebral Infarction and Outcome after Subarachnoid Haemorrhage: British Aneurysm Nimodipine Trial. *Br. Med. J.* **1989**, *298*, 636–642, doi:10.1136/bmj.298.6674.636.

7. Dayyani, M.; Sadeghirad, B.; Grotta, J.C.; Zabihyan, S.; Ahmadvand, S.; Wang, Y.; Guyatt, G.H.; Amin-Hanjani, S. Prophylactic Therapies for Morbidity and Mortality After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Network Meta-Analysis of Randomized Trials. *Stroke* **2022**, *53*, 1993–2005, doi:10.1161/STROKEAHA.121.035699.

8. Macdonald, R.L.; Higashida, R.T.; Keller, E.; Mayer, S.A.; Molyneux, A.; Raabe, A.; Vajkoczy, P.; Wanke, I.; Bach, D.; Frey, A.; et al. Clazosentan, an Endothelin Receptor Antagonist, in Patients with Aneurysmal Subarachnoid Haemorrhage Undergoing Surgical Clipping: A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial (CONSCIOUS-2). *Lancet Neurol.* **2011**, *10*, 618–625, doi:10.1016/S1474-4422(11)70108-9.

9. Claassen, J.; Park, S. Spontaneous Subarachnoid Haemorrhage. *Lancet* **2022**, *400*, 846–862, doi:10.1016/S0140-6736(22)00938-2.

10. Lantigua, H.; Ortega-Gutierrez, S.; Schmidt, J.M.; Lee, K.; Badjatia, N.; Agarwal, S.; Claassen, J.; Connolly, E.S.; Mayer, S.A. Subarachnoid Hemorrhage: Who Dies, and Why? *Crit. Care* **2015**, *19*, 1–10, doi:10.1186/s13054-015-1036-0.

11. Geraghty, J.R.; Davis, J.L.; Testai, F.D. Neuroinflammation and Microvascular Dysfunction After Experimental Subarachnoid Hemorrhage: Emerging Components of Early Brain Injury Related to Outcome. *Neurocrit. Care* **2019**, *31*, 373–389, doi:10.1007/s12028-019-00710-x.

12. Hayman, E.G.; Wessell, A.; Gerzanich, V.; Sheth, K.N.; Simard, J.M. Mechanisms of Global Cerebral Edema Formation in Aneurysmal Subarachnoid Hemorrhage. *Neurocrit. Care* **2017**, *26*, 301–310, doi:10.1007/s12028-016-0354-7.

13. Rass, V.; Helbok, R. Early Brain Injury After Poor-Grade Subarachnoid Hemorrhage.

Curr. Neurol. Neurosci. Rep. **2019**, *19*, doi:10.1007/s11910-019-0990-3.

14. Sabri, M.; Lass, E.; MacDonald, R.L. Early Brain Injury: A Common Mechanism in Subarachnoid Hemorrhage and Global Cerebral Ischemia. *Stroke Res. Treat.* **2013**, *2013*, doi:10.1155/2013/394036.

15. Molyneux, A.; Kerr, R.; Stratton, I.; Sandercock, P.; Clarke, M.; Shrimpton, J.; Holman, R. International Subarachnoid Aneurysm Trial (ISAT) of Neurosurgical Clipping versus Endovascular Coiling in 2143 Patients with Ruptured Intracranial Aneurysms: A Randomised Trial. *Lancet* **2002**, *360*, 1267–1274, doi:10.1016/S0140-6736(02)11314-6.

16. Rosen, D.S.; Macdonald, R.L. Subarachnoid Hemorrhage Grading Scales: A Systematic Review. *Neurocrit. Care* **2005**, *2*, 110–118, doi:10.1385/NCC:2:2:110.

17. Chen, H.Y.; Elmer, J.; Zafar, S.F.; Ghanta, M.; Moura Junior, V.; Rosenthal, E.S.; Gilmore, E.J.; Hirsch, L.J.; Zaveri, H.P.; Sheth, K.N.; et al. Combining Transcranial Doppler and EEG Data to Predict Delayed Cerebral Ischemia After Subarachnoid Hemorrhage. *Neurology* **2022**, *98*, E459–E469, doi:10.1212/WNL.0000000000013126.

18. Hirsch, L.J.; Fong, M.W.K.; Leitinger, M.; LaRoche, S.M.; Beniczky, S.; Abend, N.S.; Lee, J.W.; Wusthoff, C.J.; Hahn, C.D.; Westover, M.B.; et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J. Clin. Neurophysiol.* **2021**, *38*, 1–29, doi:10.1097/WNP.0000000000000806.