Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome

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ABSTRACT

Objective: To assess the relationship between seizure burden on continuous EEG (cEEG) and functional as well as cognitive outcome 3 months after subarachnoid hemorrhage (SAH).

Methods: The study included all consecutive patients with a spontaneous SAH admitted to the Columbia University Medical Center Neurological Intensive Care Unit and monitored with cEEG between 1996 and 2013. Seizure burden was defined as the duration, in hours, of seizures on cEEG. Cognitive outcomes were measured with the Telephone Interview for Cognitive Status (TICS, ranging from 0 to 51, indicating poor to good global mental status).

Results: Overall, 402 patients with SAH were included with a median age of 58 years (interquartile range [IQR] 46–68 years). The median duration of cEEG monitoring was 96 hours (IQR 48–155 hours). Seizures were recorded in 50 patients (12%), in whom the median seizure burden was 6 hours (IQR 1–13 hours). At 3 months, in multivariate analysis, seizure burden was associated with unfavorable functional and cognitive outcome. Every hour of seizure on cEEG was associated with an odds ratio of 1.10 (95% confidence interval [CI] 1.01–1.21, $p = 0.04$) to 3-month disability and mortality, and the TICS-score decreased, on average, by 0.16 points (adjusted coefficient -0.19 , 95% CI -0.33 to -0.05 , $p = 0.01$).

Conclusion: In this study, after adjusting for established predictors, seizure burden was associated with functional outcome and cognitive impairment 3 months after SAH. *Neurology*® 2016;86:253–260

GLOSSARY

cEEG = continuous EEG; CI = confidence interval; ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin Scale; NCSE = nonconvulsive status epilepticus; NCSZ = nonconvulsive seizures; OR = odds ratio; PED = periodic epileptiform discharge; SAH = subarachnoid hemorrhage; SHOP = Subarachnoid Hemorrhage Outcomes Project; TICS = Telephone Interview for Cognitive Status.

Seizures are seen in 10%–30% of critically ill patients undergoing continuous EEG (cEEG) and the vast majority of these are nonconvulsive.^{1,2} Among patients with subarachnoid hemorrhage (SAH), the presence of nonconvulsive status epilepticus (NCSE) is associated with a higher mortality at 3 months, with more than 90% of patients with SAH and NCSE dying within 3 months from SAH onset.^{3,4} Seizure prophylaxis is controversial, and most prior studies have not investigated the incremental impact of ongoing seizures—also known as the seizure burden—in patients with SAH.⁵ The argument for aggressive treatment of established nonconvulsive seizures (NCSZ) must take into account the impact of ongoing seizures on outcome, which is poorly understood and not yet studied in adults. One prior study in critically ill children found that seizure burden is associated with worse neurologic outcome.⁶

We studied the relationship between seizure burden and functional as well as cognitive outcome 3 months after onset of SAH.

METHODS **Standard protocol approvals, registrations, and patient consents.** This study was conducted according to the principles expressed in the Declaration of Helsinki and approved by the institutional review board. All patients or their health care proxies provided written informed consent for the collection of data and subsequent analyses.

From the Department of Neurology (G.M.D.M., D.P., E.M., A.V., S.S., S.P., M.C.F., S.A., S.M., J.M.S., E.S.C., J.C.), Division of Neurocritical Care, College of Physicians and Surgeons, Columbia University, New York, NY; the Department of Neurology (G.M.D.M.), University Hospital Basel, Switzerland; and the Department of Medicine, Division of Neurology (S.S.), Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Participants and study design. All patients 18 years or older with a spontaneous SAH admitted to the Columbia University Medical Center Neurological Intensive Care Unit from October 1996 through May 2013 were offered enrollment into the Columbia University SAH Outcomes Project (SHOP), a prospectively maintained clinical SAH database. We then cross-matched the SHOP database with the cEEG database, and included patients who underwent continuous EEG monitoring for at least 12 consecutive hours. The study design is retrospective.

cEEG recording. The primary indication for obtaining cEEG was to screen for NCSZ, and to monitor for changes consistent with delayed cerebral ischemia.^{4,7} cEEG was recorded digitally using 21 electrodes according to the International 10–20 System. Recordings were reviewed at least twice daily by a board-certified electroencephalographer. Two board-certified neurologists (G.M. D.M. and D.P.) reviewed all the EEG reports for data abstraction.

cEEG features. Seizures were defined as any rhythmic ictal event, defined as any spikes, sharp waves, or sharp-slow wave complexes lasting for 10 seconds or more at either a frequency of at least 3 per second or, if lower, of at least 1 per second and with clear evolution in frequency, morphology, or location. NCSE was defined as seizure lasting for 5 consecutive minutes or more.³ Seizure burden was defined as the total amount of recorded time spent seizing on cEEG (in hours).

Clinical definitions. Severity of admission neurologic grade was assessed using the Hunt-Hess and World Federation of Neurological Surgeons SAH grading scales.^{8,9} By convention, we used the Hunt-Hess scale as the primary instrument for grading neurologic impairment, with grades 1, 2, and 3 classified as good grade and grades 4 and 5 (stupor and coma, respectively) as poor grade. CT scans were evaluated by study neurointensivists for extent of initial bleeding using the modified Fisher Scale,¹⁰ Hijdra SAH score,¹¹ intraventricular hemorrhage score,¹² and volume of space-occupying subarachnoid or intraparenchymal clot using the ABC/2 method.¹³ Hydrocephalus was classified as present or absent based on the bicaudate index according to the upper limit of normal for decile of age.¹⁴ Medical and surgical management was otherwise performed as described previously.¹⁵ Following institutional protocol, prophylactic antiepileptic medication was administered for 1 week after SAH, which was then discontinued unless seizures had been recorded on EEG.¹⁶ Phenytoin was the preferred drug until 2005, i.e., until the publication by Naidech et al.¹⁷ associating phenytoin with worse cognitive outcomes. Following the publication, levetiracetam became the prophylactic drug of choice. Isolated scalp seizures were initially treated with phenytoin or levetiracetam and status epilepticus with midazolam infusions. Periodic epileptiform discharges (PEDs) were not considered seizures and there was no attempt made to eliminate them with medications; however, patients with PEDs were maintained on anticonvulsants to prevent seizures.

Outcomes assessment. At 3 months, trained personnel assessed functional outcome with the modified Rankin Scale (mRS) and cognitive outcome with the Telephone Interview for Cognitive Status (TICS) by in-person or telephone interview. The mRS is a validated 7-point scale categorizing outcome as (0) no neurologic deficits, (1) no significant disability, (2) slight disability, (3) moderate disability (requires assistance in activities of daily life, but able to walk unassisted), (4) moderately severe disability (requires assistance in activities of daily life and unable to walk unassisted), (5) severe disability (bedridden, incontinent), (6) dead. The TICS evaluates orientation, attention, language, long-term

memory, motor function, and verbal memory and is scored from 0 (worst) to 51 (best).¹⁸ All personnel assessing outcome were blinded to the cEEG findings including seizure burden.

Statistical analysis. Discrete variables were expressed as counts (percentages) and continuous variables as medians (interquartile range [IQR]). Frequency comparisons for categorical variables were performed by Fisher exact test. Two-group comparisons of continuous variables were performed with the Mann-Whitney *U* test.

Two sets of multivariate models with different outcome measures were run. First, a multivariable logistic regression model was performed assessing the association between seizure or seizure burden and unfavorable functional outcome (mRS 4–6) at 3 months after adjusting for established outcome predictors.¹⁵ To take into consideration the effect of time across the 17 years of the study, we also adjusted for the year of study inclusion.

Second, a multivariable linear regression model was run assessing the association between global cognitive outcome (TICS) at 3 months and seizure or seizure burden after adjusting for established predictors of cognitive outcome. To take into consideration the switch of the preferred anticonvulsive agent from phenytoin to levetiracetam, we adjusted for the study inclusion period before vs after 2005. All statistical tests were 2-tailed, and we considered a *p* value <0.05 as statistically significant. Stata version 12 was used for statistical software.

RESULTS Patients. From October 1996 through May 2013, 402 SAH patients underwent cEEG for an average duration of 96 hours (IQR 48–155), totaling 5.75 patient-years of cEEG. Seventy percent of patients were women, 60% were of nonwhite ethnicity, and the median age was 58 years (IQR 46–68). Fifty patients (12%) had seizures on cEEG, 46 of which (92% or 11% of the whole cohort) had NCSE and 4 NCSZ (8% or 1% of the whole cohort). All seizures were nonconvulsive. Patients with seizures were more frequently women (84% vs 68%, *p* = 0.02), older (66 years [IQR 56–74] vs 57 years [IQR 46–66], *p* < 0.001), and monitored longer (174 hours [120–373] vs 86 hours [46–142], *p* < 0.001) than patients without seizure (table 1). On admission, patients with subsequent seizures on cEEG were not more disabled than patients without seizures (Hunt-Hess 4–5 46% vs 56%, *p* = 0.23), nor did they show more frequently a thick clot in the basal cisterns (modified Fisher score 3–4 64% vs 66%, *p* = 0.57) or intracerebral hemorrhage (28% vs 27%, *p* = 0.58). When present, seizures on cEEG lasted for 6 hours on average (IQR 1–13).

Functional outcome at 3 months. At 3 months, information on functional outcome was available for 308 patients (77%), of whom 178 (58%) were either disabled or dead. Unfavorable outcomes were more frequent among patients with seizures (81% vs 54%, *p* = 0.001) (table 2). The detection of any seizure on cEEG (NCSZ or NCSE) was associated with more than threefold elevated odds of unfavorable outcome at 3 months (odds ratio [OR] 3.67, 95% confidence

Table 1 Patient characteristics

	All patients (n = 402)	With seizures on cEEG (n = 50)	No seizures on cEEG (n = 352)	p Value
Women, n (%)	282 (70)	42 (84)	240 (68)	0.02
Age, y, median (IQR)	58 (46–68)	66 (56–74)	57 (46–66)	0.001 ^a
Nonwhite ethnicity, n (%)	242 (60)	30 (60)	212 (60)	1.0
cEEG duration, h, median (IQR)	96 (48–155)	174 (120–373)	86 (46–142)	<0.001 ^a
Seizure burden (seizure duration on cEEG), h, median (IQR)	0 (0)	6 (1–13)	NA	NA
Hunt-Hess grade, n (%)				0.23 ^b
1: Mild headache	27 (7)	6 (12)	21 (6)	
2: Severe headache	45 (11)	4 (8)	41 (12)	
3: Lethargy, mild focal deficits	111 (28)	17 (34)	94 (27)	
4: Stupor	121 (30)	12 (24)	109 (31)	
5: Coma	98 (24)	11 (22)	87 (25)	
Modified Fisher grade, n (%) ^c				0.57 ^b
1: No thick cisternal blood, –IVH	64 (16)	12 (24)	52 (15)	
2: No thick cisternal blood, +IVH	72 (18)	5 (10)	67 (19)	
3: Thick cisternal blood, –IVH	148 (37)	12 (24)	136 (39)	
4: Thick cisternal blood, +IVH	114 (28)	20 (40)	94 (27)	
Aneurysmal SAH	363 (90)	45 (90)	318 (90)	1.0
Aneurysm size >10 mm, n (%)	75 (19)	14 (28)	61 (17)	0.08
Hydrocephalus, n (%)	271 (67)	30 (60)	241 (68)	0.43
Intracerebral hemorrhage, n (%)	108 (27)	14 (28)	94 (27)	0.58
Intracerebral hemorrhage, mL, median (IQR)	10 (5–29)	5 (2–18)	12 (5–33)	0.10
IVH sum score, ^d median (IQR)	3 (0–5)	2 (0–5)	3 (0–5)	0.95
Hijdra SAH sum score, ^e median (IQR)	19 (11–24)	19 (10–24)	19 (11–24)	0.75
APACHE-II score, ^f median (IQR)	18 (11–23)	18 (12–24)	18 (11–23)	0.71

Abbreviations: APACHE-II = Acute Physiology and Chronic Health Evaluation II; cEEG = continuous EEG; IQR = interquartile range; IVH = intraventricular hemorrhage; NA = not applicable; SAH = subarachnoid haemorrhage.

Because of rounding, percentages may not total 100.

^a Significant.

^b p Values were calculated dichotomizing the modified Fisher score into low grade (1–2) and high grade (3–4), and Hunt-Hess into low grade (1–3) vs high grade (4–5).

^c In 4 patients, the initial CT scan was not available to determine the modified Fisher score.

^d Range: 0, no IVH; 12, all ventricles completely filled with IVH.

^e Range: 0 = no blood; 30 = complete filling of all cisterns and fissures.

^f Range: 0–71. Higher scores indicate more severe disease.

interval [CI] 1.34–10.1, $p = 0.01$) after adjusting for established predictors of outcome (tables 3, e-1 on the *Neurology*[®] Web site at Neurology.org). In the same logistic regression model, the magnitude of association between NCSE and unfavorable functional outcome at 3 months was even stronger (OR 4.84, 95% CI 1.53–15.26, $p = 0.007$). Seizure burden was also associated with worse functional outcome in the multivariate analysis (OR 1.10, 95% CI 1.01–1.21, $p = 0.04$) after adjusting for established predictors of functional outcome (tables 3, e-2, figure, A).

Refractoriness could not be fully evaluated, as detailed information on whether NCSE responded to standard treatment regimens was not available for the whole cohort. At least 17 patients had refractory

NCSE treated with an anesthetic drug, and they all had a mRS score of 5–6 at 3 months.

Cognitive outcome at 3 months. At 3 months, cognitive evaluation by TICS was available for 121 patients (30.1%). Among these 121 patients, 11 (9.1%) had at least one seizure on cEEG. Detection of at least one seizure on cEEG was not significantly associated with the TICS score at 3 months after adjusting for predictors of cognitive outcome including age, Hunt-Hess, nonwhite ethnicity, education, study inclusion in 2005 or later (study period with levetiracetam preferred over phenytoin), and other predictors of cognitive outcome (tables 3, e-3). Seizure burden, however, remained significantly associated with TICS

Table 2 Univariate analysis for 3-month outcome

	All patients (n = 402)	With seizures on cEEG (n = 50)	No seizures on cEEG (n = 352)	p Value
Modified Rankin Scale, n (%)^a				0.001 ^b
0: No symptoms	3 (1)	1 (2)	2 (1)	
1: No significant disability	39 (13)	3 (7)	36 (14)	
2: Slight disability	46 (15)	2 (5)	44 (17)	
3: Moderate disability	42 (14)	2 (5)	40 (15)	
4: Unable to walk, needs help for own bodily needs	41 (13)	5 (12)	36 (14)	
5: Bedridden	40 (13)	11 (26)	29 (11)	
6: Dead	97 (31)	18 (43)	79 (30)	
TICS score, median (IQR)^c	31 (23–35)	30 (0–42)	31 (24–35)	0.99

Abbreviations: cEEG = continuous EEG; IQR = interquartile range; mRS = modified Rankin Scale; OR = odds ratio; TICS = Telephone Interview for Cognitive Status.

Because of rounding, percentages may not total 100. TICS ranges from 0 to 51, indicating poor to good global mental status.

^a At 3 months, the mRS was available for 308 patients (77%). Percent refers to the patients with available mRS at 3 months.

^b The p value was calculated dichotomizing the mRS into unfavorable (4–6) and favorable outcome (0–3).

^c The reported TICS results refer to the patients who were evaluated with TICS at 3 months (n = 121, 30%).

at 3 months after adjusting for age, Hunt-Hess, and study inclusion in 2005 or later, and other predictors of cognitive outcome. For every hour of seizure on cEEG, the TICS score decreased, on average, by 0.19 points (adjusted coefficient -0.19 , 95% CI -0.33 to -0.05 , $p = 0.01$) (tables 3, e-4, figure, B).

DISCUSSION Seizures occurred in 12% of SAH patients monitored with cEEG, whose main indication was screening for cerebral ischemia or NCSZ. All seizures were nonconvulsive, and would therefore have been undetected without cEEG. Both the presence of NCSZ and seizure burden were significantly associated with higher odds of an unfavorable functional outcome 3 months after SAH. Cognitive outcome at 3 months was, however, associated only with seizure burden and not just presence of NCSZ. The more subtle effect of seizure burden on cognitive outcome suggests that treatment strategies to decrease the seizure burden are warranted independent of the question of seizure prophylaxis.

The frequency of NCSZ observed in the present cohort of SAH patients is in line with the frequency reported in intensive care unit (ICU) populations at large. In 2 previous retrospective studies on unselected comatose ICU patients monitored with EEG, the frequency of NCSZ ranged between 8%² and 19%,¹⁹ with the 2 most common related diagnoses being hypoxic-ischemic encephalopathy² and epilepsy-related seizures.¹⁹ Two studies focused on patients with SAH, whereby the reported frequency of NCSE varied greatly. Among 389 patients with spontaneous SAH, 11 (3%) had evidence of NCSE

on cEEG. But since cEEG was not performed in all comatose or poorly responsive patients, the real frequency of NCSE was likely higher.²⁰ In the second study, only SAH patients with a Hunt-Hess IV–V were considered for cEEG, so that the reported frequency of NCSE (31%) likely overestimated the frequency of NCSE among SAH patients at large.²¹ The diverging findings suggest that the selection of patients for cEEG monitoring is crucial.

SAH patients with seizures were, on average, 9 years older than those without seizures (66 vs 57 years), a finding in line with the previous studies on NCSE in patients with SAH (14 years older [68 years vs 54 years]²¹ and 15 years older [68 years vs 53 years]²⁰). These findings suggest that the diagnostic yield of cEEG will be higher among older SAH patients. Reasons are speculative on why advanced age emerged as a risk factor for seizures in SAH patients. It is possible that subarachnoid blood may—through contact with an atrophic cortex—uncover a latent susceptibility to seizures. The older age observed among SAH patients with NCSZ differs from the ICU population at large, where younger age emerged as a risk factor for NCSZ.¹⁹

The magnitude of association between presence of NCSZ on cEEG and functional outcome at 3 months was clinically relevant, as patients with seizures had more than 3 times higher odds of disability or death after adjusting for established outcome predictors. This finding confirms prior reports associating NCSZ with poor outcome in SAH,^{1,4} in intracerebral hemorrhage,²² and in cerebral anoxia due to cardiac arrest.^{23,24} The mechanisms linking NCSZ to

Table 3 Outcome at 3 months

	Adjusted OR	95% Confidence interval	p Value
Unfavorable functional outcome at 3 mo (mRS 4–6) and detection of any seizure on cEEG (multivariate logistic regression model)			
Any seizure detected on cEEG	3.67	1.34–10.1	0.01
Age, per year	1.05	1.03–1.07	<0.001
Hunt-Hess, per grade	2.14	1.60–2.85	<0.001
Aneurysm size >10 mm	2.20	1.01–4.78	0.04
Unfavorable functional outcome at 3 mo (mRS 4–6) and seizure burden (multivariate logistic regression model)			
Seizure burden (1 h of seizure on cEEG)	1.10	1.01–1.21	0.04
Age, per year	1.05	1.03–1.07	<0.001
Hunt-Hess, per grade	2.16	1.61–2.90	<0.001
Aneurysm size >10 mm	2.45	1.13–5.33	0.02
	Adjusted coefficient	95% Confidence interval	p Value
Global cognitive outcome at 3 mo (TICS score) and detection of any seizure on cEEG (multivariate linear regression analysis)			
Any seizure detected on cEEG	–4.03	–11.37 to 3.32	0.28
Age, per year	–0.15	–0.29 to –0.01	0.04
Hunt-Hess, per grade	–2.23	–4.17 to –0.29	0.02
Nonwhite ethnicity	–3.20	–7.45 to 1.05	0.14
Highest education: high school or less	–3.79	–7.81 to 0.23	0.06
Global cognitive outcome at 3 mo (TICS score) and seizure burden (multivariate linear regression analysis)			
Seizure burden (1 h of seizure on cEEG)	–0.19	–0.33 to –0.05	0.01
Age, per year	–0.12	–0.26 to 0.02	0.09
Hunt-Hess, per grade	–2.08	–3.94 to –0.21	0.03
Nonwhite ethnicity	–3.68	–7.82 to 0.46	0.08
Highest education: high school or less	–3.56	–7.48 to 0.36	0.08

Abbreviations: cEEG = continuous EEG; mRS = modified Rankin Scale; OR = odds ratio; TICS = Telephone Interview for Cognitive Status.

The models also include the following covariates: aneurysmal vs nonaneurysmal subarachnoid hemorrhage, infection, pneumonia, cerebral edema, delayed cerebral ischemia, year of study inclusion (for the 2 models with functional outcome as endpoint), and inclusion on 2005 or later (for the 2 models with global cognitive outcome as endpoint). The full models are summarized in tables e-1 through e-4.

functional outcome are unclear, but recent reports contributed to our understanding of this association. Acute brain injury triggers a proinflammatory cascade,^{25–27} altering blood–brain barrier permeability and resulting in a proconvulsive state. NCSZ increase the brain’s metabolic demand, which—if unmet—may result in secondary brain injury, as evidenced by rising markers of metabolic crisis and injury, such as an elevated cerebral lactate-pyruvate ratio and glutamate.³ In turn, NCSZ can contribute to cerebral inflammation, leading to a vicious cycle between inflammation and NCSZ.¹⁶ NCSZ may be a surrogate marker for the underlying brain injury that would best be addressed—also considering the recent concerns regarding IV anesthetics as treatment for NCSE^{28,29}—by treatments aimed at the underlying cause of seizures, e.g., in form of anti-inflammatory therapies.

Every hour of NCSZ was associated with a 10% higher odds of disability or death at 3 months. This finding is in line with a recent prospective observational study among critically ill children, whereby seizure burden was associated with short-term neurologic decline, defined as in-hospital mortality and the difference between the Pediatric Cerebral Performance Category score before hospital admission and hospital discharge.⁶ The probability of neurologic decline rose sharply above a maximum hourly seizure burden of 12 minutes, when a neurologic decline occurred in 98% of children. Beyond obvious differences in the age of the study population, our study differed from this study in several points including underlying etiology, seizure frequency, and outcome measures. The prior study investigated a cohort of children with mixed etiologies with the most common diagnosis being hypoxic ischemic encephalopathy. The frequency of seizures (93/259

Figure Predicted outcomes at 3 months relative to seizure burden

(A) Predicted functional outcome. The plot was generated fitting the logistic regression model (table e-2) with the typical characteristics of subarachnoid hemorrhage (SAH) patients with seizures drawn from table 1 (66 years old, Hunt-Hess grade of 3, aneurysm present, aneurysm size <10 mm, no pneumonia, with global cerebral edema, and no delayed cerebral ischemia). (B) Predicted cognitive outcome. The plot was generated fitting the linear regression model (table e-4) with the typical characteristics of SAH patients with seizures drawn from table 1 (66 years old, nonwhite ethnicity, high school as the highest education, Hunt-Hess grade of 3, included in 2005 or later, aneurysm present, aneurysm size <10 mm, no pneumonia, with global cerebral edema, and no delayed cerebral ischemia). (A, B) The shaded area represents the 95% confidence intervals. cEEG = continuous EEG; mRS = modified Rankin Scale; TICS = Telephone Interview for Cognitive Status.

children or 36%) in the pediatric study was 3 times higher than observed in the present study, and a lack of 3-month follow-up does not allow us to understand whether the seizure burden was associated with 3-month functional outcome. Another prospective observational study of non-neonatal children admitted to a pediatric ICU showed that NCSZ were not associated with neurologic decline, while NCSE was, underscoring the relevance of seizure burden for short-term functional outcome.³⁰

The observed significant association between seizure burden and cognitive outcome—similar to a dose-effect relationship—suggests that NCSZ injure the brain along a continuum rather than a threshold effect. This is supported by a retrospective cohort study on neonates, where the number of NCSZ was associated with poor neurodevelopmental outcome.

In particular, neonates who met at-risk criteria for seizures and who had more than 75 NCSZ had a 3.9 times higher risk of microcephaly and a 6.5 higher risk of cerebral palsy than at-risk neonates with 1–75 NCSZ.³¹ Similarly, another study on 38 neonates in an ICU showed that NCSZ lasting for longer than 10 minutes per EEG recording hour had higher odds of adverse neurodevelopmental outcome than neonates with shorter seizures.³²

The study has several limitations. The retrospective design did not allow us to standardize the selection criteria for cEEG monitoring. Patients with impaired neurologic examination such as Hunt-Hess 4–5 were more likely to be monitored as NCSZ and delayed cerebral ischemia more likely to go clinically undetected if they occurred. EEG recordings were not viewed continuously but were reviewed at least twice daily. Longer seizures may be due to delayed recognition and delayed treatment, resulting in increased seizure refractoriness. In the present study, 54% of patients had Hunt-Hess 4–5 on admission, as compared to 30% of patients with Hunt-Hess 4–5 in the whole SHOP database. This may create a bias and limits the generalizability of our findings. Patients with intracerebral hemorrhages close to the cortex might have an increased risk of seizures. However, information on cortical involvement by intracerebral hemorrhage was not available to test this hypothesis. The spectrum of prescribed antiepileptic drugs changed over the years—in particular since levetiracetam was marketed—and may have influenced outcomes, as phenytoin has been linked to poor cognitive outcome after SAH.¹⁷ To address this limitation, we adjusted all the multivariate models for the year of study inclusion. Information on refractoriness was limited, so that a full evaluation of the impact of refractory NCSE on outcome was not possible. Data on neuropsychological outcome were available only for one-third of the cohort, and were missing particularly among patients with unfavorable functional outcomes, as neurologic deficits often prevented a neuropsychological evaluation with the TICS. To measure neuropsychological outcomes in this cohort, we used the TICS since it has been developed and available since 1988, well before the inclusion of the first cohort patient. In the meantime, more refined assessment tools became available (e.g., Montreal Cognitive Assessment), but we kept measuring and reporting the TICS to have a uniform and comparable measure of neuropsychological outcomes across the whole study cohort and years. Missing follow-ups were more frequent by 8% points in the group without than with seizures, and this may limit the generalizability of the study findings.

Among adult SAH patients, after adjusting for established predictors of outcome, the detection of NCSZ on cEEG is linked to functional outcome at 3 months, but not to cognitive outcome. Seizure

burden is linked to both functional and cognitive outcome. Future clinical trials on antiepileptic drugs in SAH patients should include both functional and cognitive outcome measures as primary endpoints. The association between NCSZ and functional outcomes may justify preventive antiepileptic treatments in SAH patients but may also suggest that treatments to prevent seizure occurrence should be developed to treat the underlying cause (i.e., inflammation) rather than the symptom (i.e., seizures). The incremental effect of seizure burden on functional and cognitive outcome supports detection of NCSZ using cEEG and treatments aimed at minimizing duration of seizures.

AUTHOR CONTRIBUTIONS

Gian Marco De Marchis: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content. Deborah Pugin: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Emma Meyers: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Angela Velasquez: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Sureerat Suwatcharangkoon: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Soojin Park: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. M. Cristina Faló: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Sachin Agarwal: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Stephan Mayer: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. J. Michael Schmidt: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. E. Sander Connolly: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Jan Claassen: study concept and design, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content.

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